

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

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The 2002 guidelines for the management of osteoporosis published by Osteoporosis Canada¹ identified adequate vitamin D status, in addition to calcium from diet or supplements, as essential for the prevention of osteoporosis. Since then, our knowledge of the role of vitamin D (both D₂ and D₃) in fractures, falls and other health outcomes has expanded. Canadian recommendations for vitamin D, which are more than 10 years old, have never been supported by adequately conducted dose-finding studies² and were derived primarily from early nutritional science estimates of the minimal intake necessary to prevent extreme deficiency states.

We reviewed advances in knowledge about vitamin D physiology and optimal intake requirements for adults (except in pregnancy and during lactation) to update the 2002 clinical practice guidelines. In reviewing trials of vitamin D, it is important to remember that, unlike the situation for trials of pharmacologic agents, any reported benefits of vitamin D supplementation reflect correction of a deficiency in the population under study.

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. After removal of duplicates and screening of the abstracts by two reviewers (including A.C.), 16 relevant systematic reviews remained. We included systematic reviews of randomized controlled trials and observational studies that assessed the following outcomes: fractures, falls, death or extraskelatal outcomes. We used the Assessment of Multiple Systematic Reviews instrument³ to evaluate the methodologic quality of reviews published after the cutoff date for literature reviewed in the 2002 guideline¹ until June 30, 2008 (see Appendices 1 and 2 of the full guideline,⁴ available at www.cmaj.ca/cgi/content/full/cmaj.080663/DCI). For levels of evidence and grading of the recommendations, we followed the system used in the 2002 guidelines.¹ A multidisciplinary expert panel, including the authors of this article, reviewed the identified articles. As detailed in Table 1 of the full guideline,⁴ we assigned a level of

Key points

- Vitamin D is essential for the prevention of osteoporosis.
- A serum level of 25-hydroxyvitamin D above 75 nmol/L reflects optimal vitamin D intake or synthesis to consistently improve clinical outcomes such as fracture risk; vitamin D supplementation is needed to achieve this target.
- Recommended intake for low-risk and younger adults should be increased to 10–25 µg (400–1000 IU) daily and for high-risk and older adults, to 20–50 µg (800–2000 IU) daily, with consideration of higher doses (key change from 2002 guideline).
- For individuals being treated with pharmacologic agents for osteoporosis, vitamin D status should be assessed by serum measurement of 25-hydroxyvitamin D after three months of vitamin D supplementation (key change from 2002 guideline).

evidence to each summary point (from 1 = highest to 4 = lowest), and a grade to each recommendation, according to a system that incorporated both level of evidence and expert consensus (from A = highest to D = lowest). The Guidelines Committee and the Executive Committee of Osteoporosis Canada’s Scientific Advisory Council approved the recommendations.

Assessment of vitamin D

Measurement and assay

After synthesis in the skin or ingestion through the diet, vitamin D₃ is stored in the liver, adipose tissue and muscle, where it has a half-life of about 60 days. It is converted into 25-hydroxyvitamin D₃ in the hepatocytes.^{5–7} The serum concentration of 25-hydroxyvitamin D₃ is the best indicator of the

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nutritional and functional status of vitamin D.³ It is imperative that clinical laboratories measuring 25-hydroxyvitamin D₃ participate in external proficiency testing.^{8–10} Although circulating calcitriol (1 α ,25-dihydroxyvitamin D₃ or 1,25-dihydroxycholecalciferol) is the vitamin D hormone regulating intestinal calcium and phosphate absorption, it is *not* an appropriate indicator of clinical vitamin D status in most cases.⁵ The classification of vitamin D status is outlined in Table 1. Vitamin D₂ (ergocalciferol) follows the same metabolic pathways as vitamin D₃ but may have lesser activity.⁷

Monitoring of serum 25-hydroxyvitamin D

For most Canadians, the recommendations for vitamin D supplementation outlined here should result in adequate blood levels, with no need for routine testing for vitamin D deficiency. However, in cases where deficiency is suspected (e.g., intestinal malabsorption states such as celiac disease) or where deficiency could affect the person's response to other types of therapy (e.g., in osteoporosis requiring pharmacologic therapy), vitamin D deficiency should be ruled out by measurement of serum 25-hydroxyvitamin D.

The half-life of 25-hydroxyvitamin D in the body is 15–20 days.⁶ With standard-dose supplementation, serum 25-hydroxyvitamin D plateaus after three to four months.¹¹ Therefore, to monitor a patient's response, serum 25-hydroxyvitamin D should be measured no sooner than three months after treatment begins. After administration of high-dose oral or parenteral vitamin D replacement (e.g., 500 000 IU), the peak 25-hydroxyvitamin D level may be achieved in one month.¹²

Factors associated with vitamin D deficiency

Many factors and conditions are associated with vitamin D deficiency. Some of these are causative (e.g., marked avoidance of ultraviolet radiation or malabsorption) and others are simply associated with decreased exposure to sunlight and poor nutrition (e.g., chronic illness or renal failure).^{13,14}

Sources of vitamin D

Exposure to the sun

The skin synthesizes vitamin D₃ from 7-dehydrocholesterol in response to ultraviolet B radiation in sunlight.¹⁵ This synthetic

process depends on many factors, including latitude, altitude, time of year and day, weather, age, skin pigmentation type, clothing, activity and other aspects of the environment. Production of vitamin D in the skin falls to near zero for four to five months of the year in Canada, which raises the risk for vitamin D insufficiency or deficiency.^{16–19}

Food sources

The influence of the diet on vitamin D status is minimal, given the typical daily intake of 3.7–5.9 μ g or 148–236 IU,²⁰ but it may be enough to prevent severe deficiency states, such as rickets. The few foods that naturally contain vitamin D (e.g., certain fish) are not consumed regularly. Consequently, Canadians depend on fortified dietary sources or supplements to maintain adequate vitamin D status.

Supplements

Serum 25-hydroxyvitamin D increases by 0.7–2.0 nmol/L for each 1 μ g (40 IU) of vitamin D₃ ingested daily.^{11,21} For optimal vitamin D status, adult Canadians probably require vitamin D supplementation of 20–50 μ g (800–2000 IU) daily. Doses over 50 μ g (2000 IU) can be safely administered under medical supervision.² Treatment of severe deficiency (rickets or osteomalacia) requires higher doses, e.g., 1250 μ g (50 000 IU) daily for two to four weeks, then weekly or biweekly, with monitoring of serum 25-hydroxyvitamin D at one and three months. These dosages are based on an assumption that the patient can absorb an orally administered dose.⁵

Safety and toxicity of vitamin D supplementation

Excessive use of vitamin D supplements has the potential to cause progressive accumulation and toxic effects, presenting as hypercalcemia and renal damage. Canada's "tolerable upper intake level" (the highest level of daily nutrient intake presenting no risk of adverse effects) is 50 μ g (2000 IU) vitamin D for adults.² By definition, there is no need to monitor patients' serum calcium or renal function unless doses above the tolerable upper level are administered. However, this level is undoubtedly too conservative and may eventually be revised upward, since toxic effects occur only with prolonged (at least several months) daily intake of more than 1000 μ g (40 000 IU).^{6,22}

Traditional roles of vitamin D

Effect on bone mineral density

Low bone mineral density is a risk factor for osteoporotic fracture, and vitamin D deficiency is associated with low bone mineral density.¹ Observational studies have shown an association between higher serum 25-hydroxyvitamin D (range 40–90 nmol/L) and higher bone mineral density.^{23–25} Randomized controlled trials have shown that vitamin D supplements significantly increase bone mineral density.^{26–28}

Effect on fractures

Observational studies have shown an association between low 25-hydroxyvitamin D and fractures. Clinical trials of vitamin D supplementation have been plagued by methodological issues: lack of determination of optimal dose, poor adherence,

Table 1: 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

*Reproduced, with permission, from Hanley et al.⁴

†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."

inadequate assessment of vitamin D status before or after supplementation and concurrent intervention with other osteoporosis therapies. However, it appears that 20 µg (800 IU) vitamin D₃ given daily in combination with calcium reduces the risk of hip and nonvertebral fractures, especially for elderly patients living in institutions.^{28–33}

Effect on falls

Vitamin D may improve muscle strength and lower-extremity function, but the results of studies of fall prevention are inconsistent, because of differences in populations, doses and methods of capturing data on falls.^{31,34–37} One meta-analysis suggested that vitamin D₃ at a daily dose of 20 µg (800 IU) reduced the risk of falling, particularly in trials that adequately documented the ascertainment of falls.³⁸

Nontraditional roles of vitamin D

Calcitriol is produced locally from circulating 25-hydroxyvitamin D in many tissues (e.g., skin, colon, prostate, breast, pancreas, heart and immune system), a process that is not regulated by serum calcium, phosphate or parathyroid hormone.⁵ Many important physiologic actions of vitamin D outside the musculoskeletal system are now being explored. For example, vitamin D may have important antiproliferative and prodifferentiation properties.^{5,39} Observational studies have shown a relationship between sufficient vitamin D status and lower risk of cancers.^{40–42}

Vitamin D may lower blood pressure by downregulating the production of renin. It may also stimulate the production and secretion of insulin and modulate immune function.⁵ In epidemiologic studies, low circulating levels of vitamin D were associated with increased risk of multiple sclerosis.⁴³ Vitamin D-dependent processes affect macrophage lysis of *Mycobacterium tuberculosis*.⁴⁴ Epidemiologic studies have linked vitamin D deficiency in early life with later onset of diabetes mellitus.⁴⁵

The nontraditional actions of vitamin D have not been investigated to the same extent as its effects on mineral metabolism. There has been a paucity of intervention studies to test hypothesized benefits, and none of the studies to date used sufficient doses of vitamin D or were adequately powered. Systematic reviews or meta-analyses of the available literature are therefore unlikely to provide answers in this area. A prime example is the recently released, exhaustive report of the Agency for Healthcare Research and Quality,³³ a systematic review of the evidence for vitamin D affecting health outcomes. This review found little or weak evidence supporting the nontraditional actions of vitamin D and could make no recommendations other than that more research is needed.

Summary statements about assessment of vitamin D levels, the safety of supplementation and the roles of vitamin D are presented in Box 1.

Approach to supplementation

Recommendations for vitamin D supplementation are outlined in Box 2. Given the limitations in our knowledge of optimal intake levels, evidence of the safety and potential

benefits of vitamin D supplementation support recommendations aiming for serum 25-hydroxyvitamin D levels above 75 nmol/L. For most Canadian adults, exposure to sunlight and dietary intake are insufficient to maintain this level through-

Box 1: Summary statements on vitamin D*

Assessment of vitamin D

1. Measurement of 25-hydroxyvitamin D in the serum (with no restrictions on the timing of collection) is the best indicator of vitamin D sufficiency² (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^{8,10} (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])¹¹ (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

1. In Canada, some vitamin D is obtained with safe exposure to the sun during the summer months^{46–48} (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^{11,18,19} (level 2 evidence).
2. A daily intake of 25 µg vitamin D₃ (1000 IU) — a safe, commonly available dose — will raise the average serum level of 25-hydroxyvitamin D by 15–25 nmol/L^{11,21} (level 2 evidence).
3. The upper level for safe vitamin D₃ intake has not been well defined but is probably as high as 250 µg (10 000 IU) daily^{11,22} (level 2 evidence). In clinical practice, supplementation with this dose of vitamin D is rarely required (level 4 evidence).

Effect of supplementation on bone mineral density, fractures and falls

1. Supplementation with vitamin D₃ and calcium increases bone density in postmenopausal women and in men over age 50 years^{24,27,28,49} (level 1 evidence).
2. Vitamin D₃ 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 (level 1 evidence). The evidence for community-dwelling individuals is less strong⁵⁰ (level 2 evidence).
3. There is evidence that supplementation with 20 µg (800 IU) vitamin D₃ daily reduces the risk of falls, particularly from trials with adequate ascertainment of falls³⁸ (level 2 evidence).

Nontraditional roles of vitamin D

1. Vitamin D insufficiency has been associated with malignancies⁴⁰ (especially colorectal cancer⁴¹), diabetes mellitus,⁴⁵ multiple sclerosis⁵¹ and impaired immune response⁴⁴ (level 3 evidence).
2. The benefits of vitamin D for these nontraditional roles are associated with 25-hydroxyvitamin D levels above 75 nmol/L^{21,40} (level 3 evidence).

*Levels of evidence are explained in detail in the full guideline.⁴ In brief, levels of evidence range from very high quality (level 1+, systematic overview or meta-analysis of randomized controlled trials) to very low quality (level 6, case series without controls).

out the year, and vitamin D supplementation is therefore indicated.¹⁷⁻¹⁹ The clinical approach can take into account three “settings,” which are based on suspicion for vitamin D insufficiency and its complications. The three settings are low risk for vitamin D deficiency, moderate risk for deficiency and receipt of pharmacologic therapy for osteoporosis.

Vitamin D₃ is the preferred supplementary form for humans, with vitamin D₂ being available for large-dose prepa-

Box 2: 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 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 D₃ 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 recommendations are explained in detail in the full guideline.⁴ In brief, grades of recommendations range from A (having level 1 or 1+ evidence plus consensus) to D (having level 4, 5 or 6 evidence and supported by consensus).

rations. Calcitriol and its analogues are prescription products with narrow margins of safety and are not advised for the prevention or treatment of osteoporosis. For most adults, a vitamin D₃ supplement at an initial daily dose of at least 20 µg (800 IU) is appropriate. This dose is unlikely to raise the average serum 25-hydroxyvitamin D level by more than 20 nmol/L.^{11,21} To achieve desirable vitamin D status (> 75 nmol/L), many individuals will require higher doses.

Because vitamin D is stored in body tissues, a larger, less frequent dose may be preferred by some patients. A weekly dose of 250 µg (10 000 IU) vitamin D₃ is available by prescription in some provinces. Some practitioners prescribe vitamin D₂ at a dose of 1250 µg (50 000 IU) monthly.

Knowledge gaps

There is need for research to better define the minimum required dose and optimal daily dose for musculoskeletal and other health benefits, as well as the tolerable upper intake level for vitamin D. There is also a need for randomized controlled trials to clarify the benefits and risks (if any) of vitamin D supplementation at that optimal dose. The purported benefits of vitamin D beyond musculoskeletal disorders should be confirmed in clinical trials.

This article has been peer reviewed.

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This article is a summary of a full review and guideline of vitamin D in adult health and disease (available online at www.cmaj.ca) 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.