Vitamin D supplementation: Recommendations for Canadian mothers and infants

Canadian Paediatric Society

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INTRODUCTION

Reports of vitamin D deficiency and rickets among Aboriginal people in Canada are not new. In 1984, Godel and Hart (1) reported on 16 Inuit infants living in high Arctic coastal communities who presented at approximately three months of age with a spectrum of illnesses that included hepatitis, rickets, hemolytic anemia and respiratory infections. Eighty-one per cent of infants had florid rickets and high alkaline phosphatase levels. Extremely low 25-hydroxyvitamin D (25[OH]D) levels of 6.8 nmol/L to 9.4 nmol/L were found in four of seven infants. Similarly, Haworth and Dilling (2) reported 48 cases of vitamin D-deficient rickets in First Nations communities in Manitoba between 1977 and 1984. A follow-up by Lebrun et al (3) found a high prevalence of deficiency, much of it related to breastfeeding and lack of supplementation.

More recently, the Canadian Paediatric Surveillance Program reported 104 confirmed cases of rickets in Canada between 2002 and 2004. A high percentage of these patients were of First Nations (13%) or Inuit (12%) descent, with 14% of Middle-Eastern origin (4). Vitamin D deficiency also continues to be a problem among Aboriginal mothers during pregnancy. This is underlined in a recent report by Weiler et al (5).

The present statement addresses the advances in knowledge and practice related to vitamin D since the Canadian Paediatric Society statement on vitamin D in 2002 (6) and makes recommendations based on these advances.

The emphasis is no longer solely on preventing rickets, which requires only a relatively small amount of vitamin D supplementation. The focus is now also on the prevention of associated childhood and adult diseases. New findings suggest that adequate vitamin D status in mothers during pregnancy and in their infants may have lifetime implications. These findings modify our knowledge and understanding of vitamin D metabolism, our basis for diagnosis of vitamin D deficiency and our recommendations for supplementation.

It is now clear that vitamin D is involved in the regulation of cell growth, immunity and cell metabolism. Vitamin D receptors are found in most tissues and cells in the body (7). The interaction of $1,25(OH)_2D$ with these receptors may result in a variety of biological responses influencing disease processes (8). Vitamin D deficiency has been linked to osteoporosis (9); asthma (10); autoimmune diseases such as rheumatoid arthritis, multiple sclerosis (11) and inflammatory bowel diseases (12); diabetes (13); disturbed muscle function (14); resistance to tuberculosis (15); and the pathogenesis of specific types of cancer (16,17) (evidence level III).

Maternal vitamin D status during gestation and lactation may influence the health status of the child later in life. Bone density in nine-year-old children (evidence level II-3) (9), the severity of asthma in three-year-old children (10) (evidence level II-2) and the susceptibility to type 1 diabetes (11) (evidence level II-2) have been linked to low vitamin D status during fetal life. Intervention trials have demonstrated that supplementation with vitamin D or its metabolites may improve blood glucose levels in diabetics and decrease symptoms of rheumatoid arthritis and multiple sclerosis (11,13) (evidence level III).

Dental caries may also have their beginnings in fetal or early newborn life. Studies suggest that infants of mothers who are vitamin D- or calcium-deficient during pregnancy may be at risk for enamel defects in primary and permanent teeth in spite of adequate supplementation later (18,19) (evidence level II-3). Aboriginal communities with a high incidence of vitamin D deficiency have an associated high prevalence of caries (20), although no studies of cause and effect have been carried out.

The purpose of the present update is to explore the implications of the latest research in vitamin D on the health of all Canadian mothers and their infants and to make recommendations based on these findings. A brief review of the nomenclature and metabolism is included for clarity.

REVIEW OF THE NOMENCLATURE AND METABOLISM OF VITAMIN D

Three systems are used interchangeably to measure vitamin D: Metric (ng/mL), International Units (IU) and Molar (nmol/L). 1 IU of vitamin D equals 25 ng (0.025 µg) or 65 pmol. Thus 400 IU of vitamin D equals 10 µg or 26 nmol (21). Vitamin D_3, which is produced in the skin of animals, and Vitamin D_2, which is of plant origin, are metabolized in a similar manner, first by 25-hydroxylation in the liver to $25(OH)D_2$ and D_3, inactive but stable forms used for defining vitamin D status, then by 1-hydroxylation in the kidney to $1,25(OH)_2D_2$ and D_3, the active but unstable forms.

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TABLE 1
Current definitions of 25-hydroxyvitamin D status

25(OH)D level	ng/mL	nmol/L
Deficient	<10	<25
Insufficient	10–30	25–75
Optimal	30–90	75–225
Pharmacological (potential adverse effects)	>90	>225
Potentially toxic	>200	>500

The definition of vitamin status has been modified as a result of research into the relationship between vitamin D, parathyroid hormone, serum calcium and bone resorption. Optimal plasma 25(OH)D levels have been defined as levels at which parathyroid hormone production (22) (evidence level II-2) and calcium reabsorption from bone are minimized, and intestinal calcium absorption is stabilized (range 75 nmol/L to 225 nmol/L [30 ng/mL to 90 ng/mL]). Levels greater than 225 nmol/L (90 ng/mL) may be associated with hypercalcemia and calcium deposition in tissues, and levels greater than 500 nmol/L (greater than 200 ng/mL) are considered toxic. Table 1 (22,23) shows current definitions of 25(OH)D status.

In practical terms, the aim is to provide enough vitamin D to normalize calcium absorption from the gut and minimize secretion of parathyroid hormone, yet not enough to result in hypercalcemia and its complications (24). Vitamin D deficiency, characterized by a low plasma 25(OH)D level, is associated with decreased calcium absorption from the gut and a tendency toward hypocalcemia.

VITAMIN D DEFICIENCY

A number of factors influence vitamin D sufficiency. Vitamin D_3 is produced from precursors in the skin in response to ultraviolet rays and is sunlight dependent. Exposure to sunlight varies considerably, and is influenced by factors such as latitude (25), skin pigmentation (26,27), clothing and the use of sunscreen to decrease this exposure. People in northern regions are particularly vulnerable to deficiency. For example, from October to March in Edmonton, Alberta (52° north), vitamin D_3 production in the skin is almost nonexistent (25) (evidence level II-2) (24). The situation is potentially even worse in the high Arctic, where many Aboriginals live. Vitamin D_3 production in the skin may be high in the summer months, but even then, the skin may be covered most of the time because of mosquitoes, black flies and other insects.

Furthermore, evidence is growing that the requirement for vitamin D at any age may be weight dependent (28,29). Plasma 25(OH)D varies inversely with body mass index (BMI) (30).

Vitamin D deficiency in mothers and their infants continues to be a problem in Canada (4,5,31). Aboriginal women appear to have a higher prevalence of vitamin D deficiency than their non-Aboriginal counterparts, despite similar dietary vitamin D intakes (5).

In 2003, Roth et al (32) (evidence level II-2) reported that 34% of two- to 12-year-old children in Edmonton had insufficient vitamin D levels (using the 25(OH)D cutoff levels of 40 nmol/L). If the higher threshold for vitamin D sufficiency of 75 nmol/L of 25[OH]D had been used, 90% (63 of 68) of the children would have been considered vitamin D insufficient. Underestimation of deficiency may apply to all except the most recent studies that use the higher threshold figure.

Skin production of vitamin D is minimized in infants, contributing to the problem. Because of the danger of skin cancer following sun damage to the skin, the Canadian Dermatology Association and Health Canada (33,34) recommend that children younger than one year of age should avoid direct sunlight and also use sunscreens, both of which have the effect of minimizing vitamin D production in the skin. Thus, supplementation with vitamin D is the only viable method of attaining optimum vitamin D status.

MATERNAL VITAMIN D DEFICIENCY AND SUPPLEMENTATION – PREGNANCY AND LACTATION

Maternal vitamin D deficiency is common in northern hemispheres (5,22-27,31,35) and is a major risk factor for vitamin D deficiency in infancy (34,36) (evidence level III). Rapid development of the fetus in the latter part of pregnancy tends to deplete maternal vitamin D as incorporation of calcium in the skeleton in the final trimester increases. Maternal deficiency may be associated not only with newborn hypocalcemia and rickets, but also with smaller size, decreased vitamin D in breast milk and dental malformations. The fetus and newborn are entirely dependent on the mother for their supply of vitamin D, which crosses the placenta and is reflected both in infant stores and in the amount of vitamin D available in breast milk. It is important that mothers have levels of vitamin D sufficient to meet their own needs and those of their infants.

How much maternal supplementation is sufficient? Health Canada has suggested 200 IU/day (5 µg/day) (34,37). The existing prenatal supplements contain 400 IU of vitamin D_3 per suggested daily dose. Subscripts refer to the type of vitamin D used – D_3 (of animal origin) or D_2 (of plant origin) (less effective as supplementation).

Evidence is accumulating that a much higher intake than the current dietary reference intake of 200 IU/day to 400 IU/day (5 µg/day to 10 µg/day) is necessary. A number of studies (38-41) have suggested the need for higher vitamin D intakes during pregnancy. A dose of 4000 IU/day maintained vitamin D sufficiency in the mother and also raised vitamin D in breast milk to the point at which there was no further need of infant supplementation (evidence level II-1) (41). Doses of this magnitude appeared safe. Even experimental doses of up to 10,000 IU/day for five months in pregnancy did not elevate levels into the toxic range (40).

Concerns have been expressed about the possibility of vitamin D supplementation producing a 'malignant' form of hypercalcemia during pregnancy (42). There are no reports of this severe condition being associated with vitamin D administration, although hypercalcemia can be induced by excessive levels of vitamin D supplementation.

VITAMIN D REQUIREMENTS DURING THE FIRST YEAR OF LIFE

Prematurity carries a high risk of vitamin D deficiency through low fetal stores and consumption of low volumes of milk, even milk in which vitamin D content per volume is considered adequate. A double-blind study by Backström et al (43) (evidence level I) suggested that 200 IU/kg/day (to a maximum of 400 IU/day) of vitamin D is sufficient to maintain vitamin D status and normal bone density in premature infants.

There are few data regarding vitamin D requirements in the full-term infant. Health Canada recommends that all exclusively breastfed, healthy, term infants in Canada receive 10 µg/day (400 IU/day), and that this should continue until the infant diet includes at least 10 µg/day (400 IU/day) from other sources (34). The Canadian Paediatric Society advocates an increase of vitamin intake to 800 IU/day for northern Native communities during the winter months (6). Infant formulas, dairy milk and fortified rice and soy beverages are fortified with approximately 400 IU of vitamin D_3 added per litre. These should be adequate sources of vitamin D as long as the infant drinks a sufficient quantity. However, soy (except soy formula), rice and other vegetarian beverages are inappropriate alternatives to breast milk, formula or pasteurized whole cow's milk in the first two years. Other food sources, such as canned salmon (530 IU/3 oz) and canned tuna (200 IU/3 oz), and northern traditional foods such as fatty fish, and aquatic mammals such as seals and polar bears, are good sources of vitamin D but are unlikely to add a significant amount of vitamin D to the infant diet because of limited amounts normally consumed.

Breast milk advocates suggest that breast milk is a complete food and that breastfed infants do not need extra vitamin D (44). This is only true if the mother has an adequate vitamin D status. However, maternal vitamin D deficiency during pregnancy and breastfeeding (4,31,45-48) is common and contributes to the low vitamin D content of breast milk. Without further supplementation, both preterm and full-term breastfed infants may be at risk for vitamin D deficiency. This risk may be minimized either by supplementing mothers with large amounts of vitamin D during pregnancy and lactation so that breast milk contains enough vitamin D for infant needs, or by supplementing the infant directly during the period of lactation. Hollis and Wagner (41) suggest that supplementation of the mother with up to 4000 IU/day of vitamin D is effective in assuring adequate vitamin D in breast milk for newborns (evidence level II-1)

Preliminary data from a recent cross-sectional study (DE Roth, personal communication) in Edmonton revealed that many infants with reported vitamin D intakes of over 10 µg/day (400 IU/day) (from diet and supplements) had 25(OH)D concentrations below 80 nmol/L during the winter. Among infants receiving vitamin D fortified formula or milk, or a vitamin D supplement, average 25(OH)D concentrations declined after six months of age, suggesting that the amount of vitamin D required to optimize vitamin D status increases with age, possibly reaching 2.5 µg/kg/day by 18 months of age (approximately 1200 IU/day if the child is 12 kg). There are little existing data on which to establish the normal 25(OH)D range in infancy; however, if further studies confirm that the optimal range is similar to adults, recommended dietary intakes may need to be substantially increased. Further prospective and pharmacokinetic studies are necessary to rigorously establish evidence-based dietary reference intakes.

VITAMIN D REQUIREMENTS IN OLDER INFANTS

There are also few studies related to vitamin status in toddlers and older infants. Because, at these ages, sun exposure probably contributes to vitamin D, the necessity for further supplementation depends on skin pigmentation, time of year, latitude and the use of sunscreen, all factors that would influence sun exposure. Among the studies, MRC Human Nutrition Research (United Kingdom) found a high degree of seasonality in 25(OH)D levels among toddlers 1.5 years to 4.5 years of age (49) in the United Kingdom. Mallet et al (50) found that 6% of four- to six-year-old children in Rouen, France (49.5° north), had vitamin D insufficiency. Among toddlers, 25(OH)D concentrations declined between 16 months and six years of age and were related to stopping vitamin D supplementation (50).

The Institute of Medicine recommends 200 IU/day of vitamin D for children one to eight years of age (21). However, in a study of children two to eight years of age, Roth et al (32) found that few of the children with intakes of 1.3 µg/kg/day (eg, 20 µg/day [800 IU/day] in a two-year-old) reached adequate levels of 25(OH)D of greater than 75 nmol/L. Data suggested that doses of up to 2.5 µg/kg/day of total vitamin D intake may be optimal. Further studies are needed to see whether the increase in vitamin D requirement with weight is linear or whether a better denominator would be either BMI (51) or body surface area.

VITAMIN D REQUIREMENTS IN ADULTS

Health Canada has suggested that the adequate intake of vitamin D for adults 19 to 50 years of age is 200 IU/day, those 51 to 70 years of age is 400 IU/day and those 71 years of age and older is 600 IU/day (52). Vieth (51) suggests that such a low intake may be inadequate (evidence level III). A minimum of 800 IU/day to 1000 IU/day may be needed, with up to 2000 IU/day to 4000 IU/day in special circumstances (53,54) (evidence level III).

DISCUSSION

There appears to be a discrepancy between vitamin D requirements based on recent research and current practice.

The dose of 400 IU/day recommended by Health Canada for healthy, term breastfed infants clearly prevents severe vitamin D deficiency (25[OH]D level less than 25 nmol/L) but it is now well accepted that optimal vitamin D status is associated with a 25(OH)D level greater than 75 nmol/L to 80 nmol/L (22-24). An intake of 400 IU/day of vitamin D may not be enough.

Studies (4,27,31,40,41,48) have confirmed the high prevalence of vitamin D deficiency among pregnant and lactating women (using either old or new cut-off 25[OH]D levels) and their breastfed infants, especially in northern latitudes. They also suggest that much higher amounts of vitamin D supplementation may be necessary than those recommended by Health Canada for pregnancy and lactation to achieve vitamin D sufficiency during this period.

What is not clear is the relationship and interaction between 25(OH)D associated with supplementation and vitamin D_3 production in the skin. Hypervitaminosis D has never been reported due to sunlight exposure. What if the plasma levels of 25(OH)D are already high at the time of sun exposure because of vitamin D supplementation? Is there an interaction between plasma 25(OH)D_3 and sunlight-induced cutaneous D_3 that prevents a further rise? Levels of 1,25(OH)D_3 do not modulate cutaneous production of vitamin D (55), but no studies have evaluated the possible effect of 25(OH)D_3.

HOW DANGEROUS IS PROLONGED HIGH-LEVEL SUPPLEMENTATION?

The tolerable upper intake level, the highest continuing daily intake of a nutrient that is likely to pose no risks of adverse health effects for infants up to one year, has been set at 1000 IU/day (34) (evidence level III). This may prove to be low but depends on further studies.

With regard to women during pregnancy and lactation, few studies using high levels of vitamin D supplementation have lasted longer than four to six months, so detailed studies of longer-term supplementation are desirable as well. The tolerable upper intake level in adults has been arbitrarily set at 2000 IU/day. However, a recent risk assessment based on a review of relevant, well-designed clinical trials of vitamin D in healthy adults by Hathcock et al (56) showed an absence of toxicity in trials that used vitamin D dosages greater than or equal to 250 µg/day (10,000 IU/day vitamin D_3) and supported the selection of this value as the upper limit for healthy adults (evidence level II-2).

> "As more and more evidence of the relationship between the level of vitamin D in diseases such as osteoporosis, cancer, diabetes, autoimmune diseases and neuromuscular disorders emerges, it is predicted that treatment with physiological doses of vitamin D_3 (between 4000 IU/day to 10,000 IU/day from all sources, including sun, food and supplements) with periodic monitoring of blood 25(OH)D (calcidiol) levels and calcium levels will become routine to maintain 25(OH)D levels of 75 to 150 nmol/L" (57).

SUMMARY

- Vitamin D deficiency is common among adults and children in Canada, and especially among Aboriginal people, many of whom live in high Arctic regions, where lack of light for much of the year and dressing for intense cold decreases the opportunity for vitamin D production in the skin. Furthermore, dependence on traditional vitamin D-rich foods has diminished.
- Infants younger than one year of age are especially vulnerable if they are breastfed (evidence level II-2) (Table 2).
- There is evidence that levels of 25(OH)D previously considered adequate are too low. Research suggests that levels of 25(OH)D in the range of 75 nmol/L to 150 nmol/L are optimal (evidence level II-3).
- There is growing evidence that the lack of vitamin D sufficiency may be involved in a variety of systemic diseases, many of which manifest later in life (evidence levels II-2, II-3 and III).
- Vitamin D deficiency is common among pregnant women. Supplementation of mothers during pregnancy and lactation with less than 1000 IU/day of vitamin D may be inadequate in maintaining optimal levels of 25(OH)D for both mothers and their infants (evidence level II-2).
- Low levels of vitamin D in human milk and the resultant low levels in nursing infants can be corrected by either supplementing mothers with relatively large doses of vitamin D during pregnancy and lactation or by supplementing infants with 400 IU of vitamin D daily (evidence level II-1).
- Evidence is growing that vitamin D requirements vary with weight and with BMI (evidence level II-3). This should be considered in setting dosage levels and in planning research.
- In infants and children living in the north, levels of supplementation of vitamin D of 400 IU/day to 800 IU/day appear safe. However, vitamin D deficiency continues to be prevalent in this group and doses may need to be increased, especially in light of the evidence that the amount of vitamin D needed for sufficiency can vary with weight or BMI. Overweight and obese children are at higher risk for vitamin D deficiency and may need a higher intake (evidence level II-3).
- There appears to be a discrepancy between our current practice and recommended intakes, which needs to be addressed.

RECOMMENDATIONS

- Because of the high level of vitamin D deficiency and insufficiency found in First Nations and Inuit peoples, special attention needs to be focused on these groups (recommendation grade A) (Table 2).

TABLE 2
Levels and grades of evidence

Level	Description
I	Evidence obtained from at least one properly randomized trial.
II-1	Evidence obtained from a well-designed, controlled trial without randomization.
II-2	Evidence obtained from a well-designed cohort or case-controlled analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from comparisons between times and places, with or without the intervention; dramatic results in uncontrolled experiments could also be included in this category.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Grade	
A	There is good evidence to recommend the clinical preventive action.
B	There is fair evidence to recommend the clinical preventive action.
C	The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision making.
D	There is fair evidence to recommend against the clinical preventive action.
E	There is good evidence to recommend against the clinical preventive action.
I	There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision making.

The task force recognizes that, in many cases, patient-specific factors must be considered and discussed, such as the value the patient places on the clinical preventive action, its possible positive and negative outcomes, and the context or personal circumstances of the patient (medical and other). In certain circumstances in which the evidence is complex, conflicting or insufficient, a more detailed discussion may be required. Data from reference 58

- Total vitamin D intake from all sources for the premature infant should be 200 IU/kg/day to a maximum of 400 IU/day (recommendation grade A). Subsequent vitamin D dosage should be 400 IU/day for all infants during the first year, with an increase to 800 IU/day from all sources between October and April north of the 55th parallel (approximate latitude of Edmonton) and between the 40th and 55th parallel in individuals with risk factors for vitamin D deficiency other than latitude alone (recommendation grade B).
- Because infants triple their weight in the first year, and given the evidence for weight-related vitamin D needs, more research is needed to establish whether higher intakes of vitamin D in infancy are desirable. Further research into weight-related vitamin D sufficiency should be carried out (recommendation grade A).
- To take advantage of cutaneous production of vitamin D, yet minimize possibility of skin damage, infants and children should be exposed to sunlight for short periods (probably less than 15 min/day) (recommendation grade B).
- Consideration should be given to administering 2000 IU of vitamin D daily to pregnant and lactating women, especially during the winter months, to maintain vitamin D sufficiency. The effectiveness of this regimen and possible side effects should be checked with periodic assays for 25(OH)D and calcium (recommendation grade A).
- Research should continue on the effectiveness of supplementation and possible side effects of supplementation of mothers during pregnancy (recommendation grade A).
- Research should be encouraged on vitamin D requirements for toddlers and older children (recommendation grade A).
- Research should also be focused on developing a cheaper, accurate and more universally available assessment of vitamin D status than the 25(OH)D assay, the current gold standard. Indicators of hypercalcemia should also be included in any investigations (recommendation grade A).

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