Vitamin D supplementation in northern Native communities

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In 1988, the Indian and Inuit Committee of the Canadian Paediatric Society (CPS) issued recommendations for vitamin D supplementation in northern native populations (1) based on reports of infants developing rickets in spite of adequate vitamin D intakes. Since then, there has been considerable related research. The purpose of the present statement is to explore whether there is a basis for a change in these recommendations.

Dietary reference intakes are a comprehensive set of nutrient references for healthy populations, established by Canadian and American scientists through a review process overseen by the National Academy of Sciences (2). There are four types of reference values.

- **Estimated average requirement (EAR):** The level of intake of a nutrient adequate to meet the needs of 50% of individuals.
- **Recommended dietary allowance (RDA):** A level of intake that can meet requirements of 97% of individuals in a group (calculated as EAR+2 SD).
- **Adequate intake (AI):** A level of intake, based on approximations or estimates, expected to meet or exceed the nutritional needs of a specific population. An AI is used when an EAR/RDA cannot be determined.
- **Tolerable upper intake level:** The highest level of intake that poses no risks to the health of individuals in a group, in effect, defining the highest safe intake. The No-Observed-Adverse-Effect-Level (NOAEL) defines the upper limit of safe dosage.

The report of the dietary reference intake expert panel on calcium and related nutrients (including vitamin D) was published in 1997 (2). An AI of 200 IU/day vitamin D for infants up to 12 months of age was based on the lowest dietary intake of vitamin D that has been associated with a mean serum 25-hydroxyvitamin D concentration greater than 25 nmol/L, the lower limit of normal. The recommended AI assumes that no vitamin D is available from sun-mediated cutaneous synthesis.

LITERATURE REVIEW AND DISCUSSION

There have been several reports of vitamin D deficiency and rickets among Canadian aboriginal groups in the Canadian arctic (3,4) as well as further south in a Manitoba aboriginal community at approximately 51° N latitude (5). On the basis of these and other studies suggesting an increased risk of vitamin D deficiency at extreme latitudes, recommendations for vitamin D supplementation were revised for northern Canadian populations. It was recommended that for northern populations, supplementation with vitamin D be increased during winter months from 400 to 800 IU/day during pregnancy and during the first few months of life (1). Published studies at the time suggested that these doses were safe. Since these recommendations were published, no instances of either vitamin D toxicity or rickets have been reported with this regimen, although there are few data on the compliance with the suggested regimen (6).

Traditionally, vitamin D intake in children has been considered only with regard to its role in the prevention of rickets. Previous recommendations suggested that a daily intake of 200 IU of vitamin D was adequate during the first year of life (AI) (2,7). However, it is becoming increasingly evident that preventing rickets should not be the only consideration in setting the vitamin D dose. These recommendations did not address seasonal variations in endogenous vitamin D production or the need for extra vitamin D to address other, more subtle effects of vitamin D deficiency, such as osteoporosis. Seasonal changes in sun exposure can have a marked effect on vitamin D sufficiency. There is a marked seasonal variation of sunlight exposure at extreme northern and southern latitudes; sunlight-induced vitamin D production in the skin may be absent for four to six months of the year. Even at lower latitudes, dark skin pigmentation (8), winter clothing, and the increased cultural use of protective clothing and sunscreens (9) may reduce vitamin D production in the skin even further. Low levels of vitamin D in breast milk may also contribute to vitamin D insufficiency in exclusively breast-fed infants (8,10,11).

A serum concentration of 25-hydroxyvitamin D below 27.5 nmol/L is considered to be the threshold to defining

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TABLE 1
Levels of evidence

Level of evidence	Description
I	Evidence obtained from at least one properly randomized trial
II-1	Evidence obtained from well-designed controlled trial without randomization
II-2	Evidence obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one centre or research group
II-3	Evidence obtained from comparisons between time 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 from expert committees
	Recommendations for preventive measures
A	There is good evidence to support this recommendation
B	There is fair evidence to support this recommendation
C	There is poor evidence to support this recommendation, but a recommendation could be made on other grounds
D	There is fair evidence to support the recommendation for exclusion
E	There is good evidence to support the recommendation for exclusion

Data from reference 39

deficiency in infants and neonates (2). Concentrations below this level, even in the absence of overt rickets, have been found to be associated with an increased prevalence of conditions such as multiple sclerosis (12), hypertension and deficient immune function (13). A strong association was found between pneumonia and nutritional rickets (7,14,15). In recent years, the emphasis has changed from a vitamin D dosage that simply protects against rickets and osteomalacia, to one that suppresses parathyroid secretion and protects against the development of osteoporosis (7,15,16). Children with a high bone density associated with vitamin D sufficiency are unlikely to develop osteoporosis later (17). To achieve these ends, adequacy of both calcium and vitamin D intakes is essential (18). But are we recommending enough? Furthermore, how safe are higher doses of vitamin D? Evidence in the literature regarding vitamin D doses was assessed, and codes reflecting reliability (Table 1) were assigned to data from study reports and to individual recommendations.

It is important to establish safe upper limits (ULs) when setting levels of supplementation to avoid hypervitaminosis D. The resulting hypercalcemia can lead to tissue calcification, renal problems that include loss of urinary concentration (19), and central nervous system dysfunction (20). Vitamin D intoxication, defined by elevated 25-hydroxyvitamin D levels of 400 to 1250 nmol/L (21), and hypercalcemia in the range of 2.82 to 4.00 mmol/L, (11.28 to 16.00 mg/dL) (normal serum calcium 2.15 to 2.62 mmol/L [8.60 to 10.48 mg/dL]), have been found to occur from intakes of 20,000 to 40,000 IU/day (22) (**II-2**), which are unlikely to be prescribed. More realistically, in an experiment to establish a safe UL, adults 21 to 60 years of age were given vitamin D supplementation in a range of 400 to 3800 IU/day for three months (23). No increase in calcium concentration was observed with doses of 2400 IU/day or less. However, with doses of 3600 IU/day or more, calcium levels were significantly increased. On the basis of these observations, the NOAEL for adults was set at 2400 IU/day. With an uncertainty factor of 1.2 built in for safety, a UL for adults of 2000 IU/day appeared to be reasonable (7). This figure may well be too low (24) (**II-2**). In a review of the literature, the lowest dose of vitamin D proven to cause toxicity in adults (22) was found to be 40,000 IU/day (**II-2**).

Studies in children (25,26) suggested a NOAEL in the first year of life of 1800 IU/day. With an uncertainty factor of 1.8 built in for safety, the UL for infants up to 12 months of age was set at 1000 IU/day (2) (**I**). Using this criterion, the dose of vitamin D of 800 IU/day advocated in the 1988 CPS statement, and reiterated here, appears to be quite safe (1) (**II-2**).

CALCIUM INTAKE

The amount of calcium in the diet must also be considered. Typical rickets has been reported with inadequate calcium intakes (27), especially among malnourished children (28-31) or among children drinking inadequate amounts of milk. Rickets was found to be associated with low milk intake as a result of milk intolerance or allergy (32). Rickets associated with low calcium intake is not necessarily vitamin D dependent. Indeed, some of these children had high levels of 1,25-dihydroxyvitamin D, suggesting adequate vitamin D status. The AI for calcium for infants up to six months of age is 210 mg (5.3 mmol)/day; for infants seven to 12 months is 270 mg (6.8 mmol)/day (2) (**III**). Inadequate calcium intake is also a factor in the development of osteoporosis. Are children getting enough calcium? Dietary surveys suggest that, except for the first year of life, they are not (7). Furthermore, with the aggressive marketing of soft drinks and especially colas, the presence of soft drink dispensers in schools, and the substitution of soft drinks for dairy products, there are serious concerns that these drinks are supplanting calcium-containing dairy products in the diet. Not only do children get less calcium, colas are high in caffeine, which contributes to demineralization especially in the absence of adequate calcium intake (33), (**II-2**). This may be setting the stage for significant osteoporosis later. Other reasons for low calcium intake in northern Canada include difficult access to and high cost of dairy products in stores, and the fact that milk and other dairy products may not be part of the local culture, eating and cooking practices.

COMPLIANCE PROBLEMS

Compliance problems may undermine the effectiveness of vitamin regimens. Noncompliance to prophylactic vitamins has been documented in aboriginal communities in Manitoba with a high prevalence of rickets (M Tenenbein, personal communication). Because of this problem, a different strategy, a program of intermittent high dose vitamin D prophylaxis, was introduced in 1995. This program called for the administration by community nurses of two doses of 100,000 IU (2.5 mg) of vitamin D during pregnancy, one at the time of pregnancy diagnosis and one at 36 weeks' gestation, in addition to routinely prescribed vitamin D-containing prenatal supplements. Their infants were given one dose of 100,000 IU of vitamin D at four weeks of age (or at the time of the first immunization) in addition to regular daily vitamin D prophylaxis of 400 IU. Anecdotally, the incidence of rickets has fallen, but there has been no biochemical or radiological follow-up to assess the safety and effectiveness of this protocol.

PULSE THERAPY

Little has been published on the subject of pulse therapy with vitamin D during infancy. Three studies suggest a potential for toxicity, especially with very large doses. Markestad et al (34) administered 600,000 IU (15 mg) ergocalciferol orally every three to five months to 41 infants, with assays two weeks later and again before the next dose. The two-week postdose levels of 25-hydroxyvitamin D were well above normal and although they returned to normal before the next dose, in 14 (34%) infants, calcium levels in the hypercalcemic range (greater than 2.8 mmol/L) were later found in one or both follow-up assays. Pietrek et al (35) gave intermittent doses of vitamin D of 300,000 IU to two groups of infants; one group was described as healthy and the other was described as 'sick' (not explained). At follow-up, high 25-hydroxyvitamin D levels of 40 µg/L and 86.2 µg/L were found. They concluded that, although high dose vitamin D was effective in preventing rickets, they were concerned about the potential for hypervitaminosis D. Misselwitz et al (36) studied 10 children (one-and-a-half to 14 years of age) with hypercalciuria and nephrocalcinosis. All had received high doses of vitamin D in infancy.

Two studies in adults using lower doses were more promising. Byrne et al (37) reviewed 11 papers dealing with vitamin D administration every six months to elderly subjects, both low dose and high dose, 100,000 IU (2.5 mg). With both regimens, follow-up 25-hydroxyvitamin D levels were normal. Similarly, Stephens et al (38) found that a dose of 100,000 IU (2.5 mg) ergocalciferol given in the fall to a group of vitamin D-depleted Asians gave a sustained rise in 25-hydroxyvitamin D level for about six months. Both of these studies on adults suggest that pulse therapy with 100,000 IU of vitamin D is safe and may be suitable where compliance is poor.

With these limitations in mind, the strategy of high dose pulse Vitamin D administration could be considered in communities at particularly high risk (**II-2,C**).

Recommendations:

- Aboriginal infants who are entirely breast-fed should be given 400 IU of vitamin D daily. This may be increased to 800 IU/day from October to April for children who live above a latitude of 55°, or at lower latitudes in communities with a high prevalence of vitamin D deficiency; for children with dark skin; and for those avoiding sunlight exposure or using sunscreens frequently. The administration of 800 IU/day should be limited to children younger than two years of age, who are at the greatest risk for rickets (39) (**II-2, A**).
- Infants who are bottle-fed with formulas made from fortified whole or canned milk have sufficient amounts of vitamin D during the summer, but should receive a supplement of 400 IU/day of vitamin D from October to April (**II-2, A**).
- Pregnant women and nursing mothers in northern Canada should take 400 IU/day of vitamin D as fortified milk or as supplementary vitamin D throughout pregnancy, in addition to their usual prenatal vitamin and mineral supplementation, for a total of 800 IU/day of vitamin D from October to April (**II-3, A**).
- Children older than two years of age who do not drink vitamin D-enriched milk should be given an additional 400 IU/day of vitamin D from October to April. The long days during the summer should provide enough sunlight to produce adequate amounts of endogenous vitamin D (**III, A**).
- Drinking soft drinks, including fruit drinks, and especially colas, should be discouraged because they contain little calcium and replace calcium-containing drinks such as milk. Colas also contain caffeine, which has been implicated in calcium loss from bone (**II-3, A**).
- School sponsorship by cola manufacturers and the presence of soft drink dispensers in schools should be discouraged because they may encourage the intake of soft drinks over dairy products (**III, B**).
- Shelves featuring soft drinks, especially colas, should be featured less prominently in stores to discourage the impulse buying of these products instead of calcium-containing dairy foods (**III, B**). Calcium-containing dairy products should be featured.
- Pulse high-dose vitamin D therapy has the potential for overcoming problems of compliance with supplementation. Further studies need to be carried out regarding its safety in children. The use of closely

monitored pulse therapy with high dose, 100,000 IU vitamin D, may be appropriate where the prevalence of rickets is high and compliance to vitamin D prophylaxis is low, but is not recommended at this time because of the lack of safety data in children (**II-2, C**).

SUMMARY

Review of the present situation suggests that the previously recommended intakes are effective and safe. Ingestion of too much vitamin D can result in vitamin D intoxication; however, recent studies suggest that the dose of vitamin D needed to cause intoxication is much higher than previously suspected. Thus, in practice, the administration of vitamin D should strike a balance between these two positions.

For northern aboriginal infants as well as for pregnant and lactating mothers, the administration of 800 IU/day, a dosage between an AI of 200 IU/day and a conservative UL of 1000 IU/day appears to be both reasonable and safe, especially during the winter months when vitamin D production in the skin is low. Because osteoporosis in adults may have its origins in infancy and childhood, attention needs to be paid to both calcium and vitamin D intake in these age groups.

There is conflicting evidence regarding the safety of high dose pulse vitamin D therapy, especially with intermittent doses of more than 100,000 IU. Therefore, pulse therapy with vitamin D should not be considered routinely until further studies in children confirm effectiveness and especially, safety.

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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