Vitamin D Insufficiency in North America

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ABSTRACT Vitamin D insufficiency is a term that has been used to describe the finding of biochemical evidence of deficiency, without obvious clinical signs or symptoms, such as rickets or osteomalacia. The condition is most commonly diagnosed by a serum 25-hydroxyvitamin D below 40 nmol/L (16 μg/L). This paper reviews North American studies addressing the prevalence of the problem, and the growing body of evidence that vitamin D insufficiency predisposes individuals to poor bone and muscle health. The term insufficiency is somewhat misleading, as patients with this condition are really just part of the spectrum of vitamin D deficiency. If the more generous definition of this condition is used (serum 25-hydroxyvitamin D < 80 nmol/L), a much larger proportion of the population has the problem. The response to vitamin D supplementation in clinical trials suggests current recommendations for dietary intake of this vitamin are too low and that a higher adequate intake should be recommended. J. Nutr. 135: 332–337, 2005.

KEY WORDS: vitamin D • rickets • osteomalacia • osteoporosis • 25-hydroxyvitamin D

In grade school, most of us were taught that childhood deficiency of vitamin D results in rickets but that it was not a major problem anymore because of widespread use of vitamin supplements and the fortification of milk with vitamin D. In medical school, most physicians learned that the adult form of vitamin D deficiency, osteomalacia, is rare and is usually associated with malabsorption syndromes or genetic disorders. However, more recent studies suggest we have been underestimating the prevalence of milder forms of vitamin D deficiency, and a reassessment of the adequate intake of vitamin D is in order.

Workers in the field of osteoporosis have begun to recognize that mild to moderate vitamin D deficiency may contribute to bone loss and muscle weakness, resulting in increased propensity to fracture and fall. In the 1990s, clinical trials demonstrated that giving elderly adults supplementation with calcium and vitamin D resulted in a reduction in the fracture rate. A number of the participants in those studies were identified as having low levels of serum 25-hydroxyvitamin D [25(OH)D]. The availability of clinical assays for 25(OH)D has made possible the assessment of vitamin D nutrition in a number of population studies, and the prevalence of vitamin D insufficiency, also termed "hypovitaminosis D" or "subclinical vitamin D deficiency," is now felt to be much greater than previously believed. The focus of this paper is on the prevalence of inadequate vitamin D nutrition in North America.

As outlined in the paper by Dr. Hollis in this symposium, the definition of normal levels of 25(OH)D has been the subject of controversy over the last 30 y (1). He makes a convincing case that the so-called normal range for 25(OH)D was probably defined in early studies by assessing a population of subjects with inadequate vitamin D nutrition or sunlight exposure. In the early days of clinical application of 25(OH)D assays, clinical laboratories published different normal ranges for winter and summer, without considering the possibility that the lower levels in winter might reflect insufficient vitamin D or that they might be associated with clinical conse-

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1 Presented as part of the symposium “Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency” given at the 2004 Experimental Biology meeting on April 18, 2004, Washington, DC. The symposium was sponsored by the American Society for Nutritional Sciences and supported in part by educational grants from the Centrum Foundation of Canada and The Coca-Cola Company. The proceedings are published as a supplement to The Journal of Nutrition. This supplement is the responsibility of the guest editors to whom the Editor of The Journal of Nutrition has delegated supervision of both technical conformity to the published regulations of The Journal of Nutrition and general oversight of the scientific merit of each article. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, editor, or editorial board of The Journal of Nutrition. The guest editors for the symposium publication are Mona S. Calvo, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, Laurel, MD, and Susan J. Whiting, College of Pharmacy and Nutrition, University of Saskatchewan, SK, Canada.

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3 Abbreviations used: 25(OH)D; 25-hydroxyvitamin D; CPBA, competitive protein binding assay; NHANES III, National Health and Nutrition Examination Survey (NHANES) III; PTH, parathyroid hormone.
sequences. More recent studies have found that as serum 25(OH)D falls in the winter months, serum parathyroid hormone (PTH) rises and bone density falls (2,3), although this observation is not confirmed in all studies (4). Further, these changes can be prevented by vitamin D dietary supplementation (3).

Critical to the use of serum 25(OH)D to define vitamin D deficiency is the reliability of the measurement. Recently, investigators have raised questions about the performance of the 25(OH)D assays in clinical laboratories and have found a disturbing lack of standardization and consistency in performance by some laboratories (5). This is further complicated by the differing methods of measuring 25(OH)D, with the 2 commonly used clinical laboratory methods RIA and competitive protein binding assay (CPBA), differing in their specificity for the vitamin D metabolite (6). The CPBA usually gives results about 20–30% higher than the RIA (7). However, these concerns about the community clinical laboratory performance of 25(OH)D assays do not negate the population studies discussed in this paper. It is important to emphasize that the measurements of 25(OH)D in population studies and large clinical trials can still be regarded as providing reliable information, because the individual subject measurement inaccuracies should be randomly distributed and the population means therefore should be accurate.

When one uses the serum 25(OH)D to define an individual's vitamin D status, it is generally accepted that a serum 25(OH)D level of <20–25 nmol/L (8–10 µg/L) identifies a patient at high risk for rickets or osteomalacia (8). The definition of vitamin D insufficiency or subclinical deficiency is more controversial. The most conservative and usual estimate of the lower limit of normal for serum 25(OH)D is 40 nmol/L (16 µg/L) (9). However, more recent evidence would suggest that this is setting the bar too low. A higher level is now favored by many workers in the vitamin D field, somewhere between 50 and 80 nmol/L (10–12). Cross-sectional population studies, graphing 25(OH)D levels vs. serum PTH, have shown that as the serum 25(OH)D falls below a level of around 75–80 nmol/L, the serum PTH begins to rise (11). In an accompanying paper in this symposium, Dr. Hollis outlines the rationale for identifying this inflection point as the level that identifies vitamin D insufficiency (1). Although we are in full agreement with this position, we recognize it is not a universally accepted definition, and, for our discussion of prevalence of vitamin D insufficiency in North America, we will use the conventional definition of a serum 25(OH)D of 40 nmol/L.

In this paper, we review studies of vitamin D levels in a variety of populations in North America. They are consistent in adding to the weight of evidence indicating that not only is vitamin D insufficiency a common problem in the more northern latitudes but frank vitamin D deficiency is being missed in a significant portion of our population. We focus on studies in the United States and Canada, because there were inadequate data on the extent of this problem in Mexico and Central America.

**Vitamin D insufficiency in North American adults**

Gloth et al. (13) measured vitamin D levels in a 116 indoor dwelling elderly individuals living either in a housebound situation in the community or in a teaching hospital-associated nursing home and compared them to a 128 healthy ambulatory controls who were part of the Baltimore Longitudinal Study on Aging. Surprisingly, 54% of the community dwelling housebound and 38% of the nursing home residents had serum 25(OH)D levels in the frank deficiency range (below 25 nmol/L). This was despite what would be considered a normal estimated dietary intake of vitamin D (normal was defined at 200 IU/d at the time of the study).

Thomas et al. (14) examined a cohort of 290 consecutive hospitalized patients on a general medical ward at the Massachusetts General Hospital in Boston, MA. Of these individuals, 57% had a serum 25(OH)D below 40 nmol/L (the lower limit of normal) and 27% were classed as “severe” deficiency, having 25(OH)D levels below 20 nmol/L. Even among those with intakes above the current recommendation for vitamin D, 43% were actually vitamin D deficient. The current recommendation of 400 IU of vitamin D per day may not be enough to prevent vitamin D deficiency in this population.

Nesby-O'Dell et al. (15) determined the prevalence and determinants of vitamin D deficiency among healthy, ambulatory, nonpregnant African-American and Caucasian American women, aged 15–49 y, who participated in National Health and Nutrition Examination Survey III (NHANES III). The final sample of 1546 African American women and 1426 Caucasian women included those who had vitamin D measurements but did not have known bone diseases or disorders that would affect vitamin D levels and were not taking supplements or medications that would affect vitamin D levels. Hypovitaminosis was defined as serum 25(OH)D = 37.5 nmol/L (15 µg/L). In both groups, the mean 25(OH)D concentrations were higher with milk or cereal consumption > 3 d/wk, the fall season, rural residence, and use of oral contraceptives. In both groups, there was a significant negative association between winter season and serum 25(OH)D. The incidence of vitamin D insufficiency and deficiency is indicated in Table 1.

Tangpricha et al. (16) examined free-living healthy men and women (60% Caucasian) in Boston, MA (42° N). They defined vitamin D insufficiency as a serum 25(OH)D of ≥20 µg/L (50 nmol/L), and divided their subjects into 4 age groups, 18–29 y, 30–39 y, 40–49 y, and ≥50 y. Serum 25(OH)D was measured in 142 subjects at the end of summer and in 165 subjects at the end of winter. A high incidence of vitamin D insufficiency was found (Table 2). A significant (P < 0.001) difference was demonstrated between measures of 25(OH)D after summer (35 ± 10 µg/L) and after winter (30 ± 10 µg/L). Vitamin D insufficiency was more prevalent in all age groups after winter and averaged 30% after winter and 11% after summer. Somewhat surprisingly, the eldest group was least likely of the groups to have insufficiency and the authors felt this is likely explained by subjects’ use of a multivitamin containing 400 IU of Vitamin D. Multivitamin use was significantly inversely associated with vitamin D insufficiency in the after summer and the after winter groups.

**TABLE 1**

<table>
<thead>
<tr>
<th>Vitamin D deficiency and insufficiency (hypovitaminosis D) in young adult Caucasian and African-American women1</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>African American</td>
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<tr>
<td>44.2 ± 1.1</td>
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<tr>
<td>Caucasian</td>
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1 Adapted from Nesby-O’Dell et al. (15).
TABLE 2
Percentage of young adults with vitamin D insufficiency

<table>
<thead>
<tr>
<th>Age groups</th>
<th>After winter</th>
<th>After summer</th>
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<tr>
<td>y</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>32</td>
<td>4</td>
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<tr>
<td>30–39</td>
<td>25</td>
<td>18</td>
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<tr>
<td>40–49</td>
<td>30</td>
<td>20</td>
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<tr>
<td>≥50</td>
<td>16</td>
<td>4</td>
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</tbody>
</table>

1 Adapted from Tangpricha et al. (16).

Evidence detailing vitamin D insufficiency in North American children is mounting. The reemergence of vitamin D deficient rickets is a surprising finding in many of North America’s medical centers. Binet and Kooh (23) reported that between the years 1988 and 1993 in Toronto, there was a total [25(OH)D <40 nmol/L] increased from 38% in the September sample to 60% in the March sample (χ² = 14.9, P < 0.001). They concluded that vitamin D deficiency and borderline vitamin D status are common among older residents of long-term care facilities in Canada. Evaluation of interventions to improve the status of vitamin D nutrition in this population is needed.

Rucker et al. (21) examined seasonal changes in parameters of calcium metabolism, in 188 ambulatory, community-dwelling adults aged over 25 y living in Calgary, Alberta (52° N latitude). Although not a large study, it was highly representative of its population base. The subjects were randomly selected from the Calgary cohort of 1065 subjects participating in the Canadian Multicenter Osteoporosis Study (22), which, in turn, selected subjects by computerized random identification in the local telephone directory. Subjects were excluded if they were taking >200 IU vitamin D daily or had frank vitamin D deficiency by serum 25(OH)D measurement (≥25 nmol/L). The typical seasonal changes in 25(OH)D were seen, but a very high proportion of the subjects had at least one level that fell in the range of vitamin D insufficiency, at least once during the year. When the 80 nmol/L minimum for adequate vitamin D 25(OH)D levels was used as the cutoff, almost all subjects fell in the vitamin D insufficiency category (Fig. 1). Because Calgary is at a much higher altitude and has a higher number of sunny days per year than any other major Canadian city, one can assume that UV B light exposure of the skin would be higher there than other communities in Canada, yet endogenous vitamin D synthesis appears to be inadequate to prevent vitamin D insufficiency in these subjects. This suggests that general recommendations for vitamin D supplementation may be appropriate.

Vitamin D insufficiency in children

Evidence detailing vitamin D insufficiency in North American children is mounting. The...
of 17 cases of clinical vitamin D deficiency rickets in children 7 to 33 mo of age. All of the patients were symptomatic and had radiographic evidence of rickets and, when supplemented with vitamin D, all recovered. Similarly, Haworth and Dilling (24) reported the incidence of vitamin D deficient rickets in Manitoba in a period ranging from 1972 through 1984. Over the 12-y observation period, there were 48 cases of rickets (aged 1 to 49 mo) admitted to the Winnipeg Children's Hospital (49° 54′ N latitude) and of those, 40 were of Canadian native ancestry (38 Indian and 2 Inuit). Kreiter et al. (25) reported that 30 African-American infants and children were diagnosed with nutritional rickets at 2 medical centers in North Carolina (34 to 36° N latitude) from 1990 to 1999. Surprisingly, over half of the cases occurred in 1998 and the first half of 1999. Vitamin D deficient rickets in children (primarily African descent) who were breast-fed has also been reported in the southern (26,27) and northern United States (28).

Common to almost all of these cases of vitamin D deficient rickets in young children is dark pigmented skin (23–28), little exposure to sunlight (23–25), little or no vitamin D supplementation in mother or child (23–27), and exclusive breastfeeding (23,25–28). Although areas of higher latitude seem to be at higher risk for vitamin D deficient rickets (23–25,28), even in lower latitudes with areas of abundant sunlight, vitamin D deficient rickets has been reported (26,27).

Laboratory investigations detailing the levels of serum vitamin D have demonstrated that a large proportion of North American children living in higher latitudes are vitamin D deficient. Lebrun et al. (29) performed a cross-sectional investigation documenting vitamin D status of a random sample of 80 mother–child pairs (child age 3–24 mo) in a Manitoba community with a high incidence of rickets. Venous blood was collected from both mother and child to determine serum 25(OH)D levels. It was found that serum 25(OH)D levels were below normal range in 43% of children and 76% of mothers. It was concluded that vitamin D levels were low in this population due to a lack of fortified dairy products and vitamin D supplements. In a similar investigation from the Northwest Territories (about 68° N latitude) of Inuit, native, and Caucasian mothers and newborns, the intakes of vitamin D and calcium were determined prenatally in the mothers and plasma concentrations of 25(OH)D and calcium were also measured in mothers and newborns at delivery (30). The mean daily intake of vitamin D was significantly higher in the Caucasian mothers compared with the Inuit or native mothers before childbirth. No supplementation with vitamin D was a significant predictor of vitamin D deficiency in all populations. At delivery, the plasma levels of 25(OH)D were significantly lower in native mothers and their newborns compared with the Caucasian mothers. Gessner et al. (31) completed a survey of the 25(OH)D levels from 133 children between the ages of 6 to 23 mo from Alaska. They found that 11% of the children had vitamin D levels in the abnormally low region (<15 μg/L) and 20% had a low-normal rating (15 to <25 μg/L). Surprisingly, children that were still breast-fed had a significantly higher probability of having low vitamin D levels. They concluded that breast-feeding in the absence of adequate vitamin D supplementation is the greatest risk factor for low circulating levels of vitamin D.

Gartner and Greer (32) developed guidelines for vitamin D intake in infants and stated that rickets in infants was attributable to inadequate dietary intake of vitamin D and/or decreased exposure to sunlight. They recommended that all infants, including those who are exclusively breast-fed, have a minimum intake of 200 IU of vitamin D per day beginning during the first 2 mo of life and that an intake of 200 IU of vitamin D per day be continued throughout childhood and adolescence. A further recommendation is that all dark-skinned breast-fed infants and children should receive vitamin D supplementation (25).

Clinical trials also suggest a high incidence of vitamin D insufficiency

Clinical trial data tend to support the concept of an optimum serum 25(OH)D level around 75 nmol/L. Chapuy et al. (33) conducted a randomized clinical trial of calcium (1200 mg/d) and vitamin D (800 IU/d) vs. placebo, in elderly French women. This study was the first randomized, placebo-controlled, clinical trial to show prevention of hip fractures. The supplementation of vitamin D caused a significant rise in serum 25(OH)D to a mean of ~100 nmol/L. In a 3-y, randomized, double-blind, placebo-controlled trial in 389 men and women over age 65, Dawson-Hughes et al. (34) demonstrated that supplementation with 700 IU vitamin D and 500 mg calcium (as citrate malate) reduced nonvertebral fractures and had a moderating effect on age-related loss of bone density. The increase in 25(OH)D was from 33 to 44.8 μg/L (82.5 to 112 nmol/L). In these 2 studies, 25(OH)D was measured by CPBA. Thus, the increase to levels over 100 nmol/L is roughly equivalent to the 70–80 nmol/L levels as measured by RIA in the treatment groups of the subsequent studies showing a positive effect of vitamin D.

A randomized trial of vitamin D supplementation in elderly ambulatory individuals achieved an average level of 25(OH)D of 74 nmol/L while demonstrating a reduction in fractures in the group receiving vitamin D supplementation (35). The Amsterdam Longitudinal Aging Study found an increased risk of sarcopenia and decreased grip strength when serum 25(OH)D was below 75 nmol/L (36). In a study testing the effect of 400 IU of vitamin D and 600 mg of calcium daily vs. placebo in a population of 122 elderly women (average age 85 y) living in a long-term geriatric care facility, Bischoff et al. (37) found a reduction in falls in the vitamin D treated group. Again, the serum 25(OH)D rose significantly in the treated group and averaged 76 nmol/L. The studies by Trivedi et al. (35) and Bischoff et al. (37) used the RIA methodology for measuring 25(OH)D.

These clinical trials clearly show a beneficial effect of vitamin D supplementation in the selected population. By inference, they also support the notion that these populations have inadequate vitamin D nutrition. In light of the clinical trial evidence of fracture prevention, the Osteoporosis Society of Canada has recommended an intake of 800 IU of vitamin D per day for men and women over age 50 (38).

Sources of vitamin D: sunlight or supplements?

There is a misconception in the general public that dietary sources of vitamin D are all that is necessary. There are very few natural food sources of vitamin D, most notably egg yolks, fatty fish, and fish-liver oils. Other sources of vitamin D in our diet include fortification of milk, margarine, and some cereals. In an excellent and detailed review, Vieth (12) calls attention to the abysmally poor level of evidence used to set the limits for national recommended dietary allowances. Current recommendations for vitamin D intake established by the Standing Committee on Dietary Reference Intake in 1997 suggested that, for the United States and Canada, adults under the age of 50 should consume 200 IU of vitamin D per day, 400 IU/d for adults between the age of 50 and 70, and 600 IU/d for
adults over the age of 70 (39). As noted above, the Osteoporosis Society of Canada recommends a higher intake, and some experts in the field would suggest even these recommendations are too low (12,38).

Dr. Hollis’s paper (1) in this symposium has outlined the importance of sunlight exposure in vitamin D synthesis. In northern latitudes, it is possible to use sunlight exposure in summer to build adequate body stores of vitamin D to last through the winter. In a study of outdoor workers, Barger-Lux and Heaney studied individuals with an average of 38 h of sun exposure per week over a 16-wk working season (40). A late summer level of 25(OH)D of 127 nmol/L was needed to achieve a serum 25(OH)D of 75 nmol/L by late winter. They concluded that most persons living in the northern United States and Canada, spending most of their daylight hours indoors, cannot generate adequate vitamin D repletion with occasional sun exposure. Clearly, they will require other substantial sources of vitamin D and, for most, that means vitamin D supplements.

Conclusions

The accumulation of evidence would suggest that vitamin D insufficiency is common in the more northern latitudes (Canada and the northern half of the United States), even when one uses the most conservative estimate of adequate levels of serum 25(OH)D (40 nmol/L). Two issues arise from this observation: 1) What should be done to reduce the prevalence of vitamin D insufficiency? 2) Should measurement of serum 25(OH)D become part of routine clinical laboratory measurements, to detect vitamin D insufficiency in the general population?

To answer the first question, it seems obvious that either increased UV B skin exposure or increased dietary intake of vitamin D is required. Because sunlight exposure in northern latitudes does not provide effective vitamin D synthesis the whole year round, increasing dietary recommendations for vitamin D intake would appear to be appropriate. The clinical trial evidence suggests that an intake of at least 800 IU of vitamin D daily is associated with improved bone and muscle health in the elderly. Heaney has provided evidence that an intake of 1000 IU/d does not cause progressive rises in serum 25(OH)D and is likely to simply maintain levels somewhere between 50 and 100 nmol/L (41). Vieth (42) has provided evidence that vitamin D toxicity is not a realistic concern with daily doses of 4000 IU/d and has suggested that the available evidence would support safety of doses up to 10,000 IU/d. It is our opinion that the lowest recommended dietary intake for vitamin D-3 for adults therefore should be at least 800 IU/d, and doses up to at least 2000 IU/d should be considered to be within a generous margin of safety. As Vieth (12) points out, the selection of 2000 IU as an upper limit of allowable safe dose by the 1997 National Academy of Sciences panel was based on a limited review of the literature, which ignored studies indicating safety of higher doses.

With respect to the second question, it is difficult to recommend widespread use of serum 25(OH)D as a clinical screening tool to screen populations for inadequate vitamin D levels in the absence of effective clinical laboratory standardization. Binkley et al. (5) and the accompanying editorial by Hollis (6) make a strong case for the urgency of pursuing this goal. Until such standardization is in place, it seems more logical to simply recommend a higher daily intake of vitamin D rather than screening populations for low 25(OH)D levels.

However, serum 25(OH)D is an appropriate clinical laboratory test for detecting frank vitamin D deficiency, when clinical clues are present. In the University of Wisconsin study, the clinical laboratory assays performed reasonably well in detecting very low levels of serum 25(OH)D. But when the levels get into the midrange, the reproducibility of the measurement is substantially decreased (5). Therefore, the clinical usefulness in monitoring an individual’s response to vitamin D supplementation is doubtful.

In summary, the prevalence of vitamin D insufficiency depends on how one defines the state of vitamin D stores, as reflected by serum 25(OH)D. Even using the most conservative estimate, it appears that the problem is widespread, particularly in individuals with darker skin pigmentation and the elderly living above 30° N latitude. The available evidence suggests a need for an increase in our estimation of an adequate intake of vitamin D, probably to a level of at least 800-1000 IU/d (20–25 μg/d).

LITERATURE CITED


