Vitamin D: Balancing Cutaneous and Systemic Considerations

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Abstract

Background. Vitamin D insufficiency may lead to various health problems. By encouraging sun protection to prevent skin cancer, physicians may be limiting a major source of vitamin D for many individuals.

Methods. We did a literature review on issues related to vitamin D inadequacy, particularly those relevant to various racial/ethnic groups.

Results. Vitamin D is an important hormone with many physiologic roles beyond those related to bones, including blood pressure regulation and acting as a tumor suppressant. The recommended amount of vitamin D has recently increased for adults over age 50. Moreover, some researchers are urging higher doses for the entire population to prevent osteoporotic fractures.

Conclusions. Previous studies that have found serum levels of vitamin D in their sun-protected subjects to be in the normal range may need to be reevaluated. In concert with counseling sun protection, physicians should consider discussing vitamin D intake, typically in the form of supplements.

Endogenous vitamin D production begins with ultraviolet B (UVB) radiation interacting with the skin; therefore, avoidance of UVB radiation can potentially result in vitamin D deficiency. However, such avoidance is a cornerstone of the prevention of skin cancer.[1] Nonmelanoma skin cancer, which is linked to cumulative sun exposure, is the most common malignancy in the United States.[1] Furthermore, the incidence of malignant melanoma, associated with intermittent high-intensity sun exposure, has risen dramatically. In 1981, an American's estimated lifetime risk of malignant melanoma was 1 in 250; as of 1996, that risk had soared to 1 in 87.[2,3] To prevent melanoma and nonmelanoma skin cancers, many physicians urge sun avoidance when UVB radiation is most intense, in combination with protective clothing and use of sunscreen.[4]

Some studies suggest that small amounts of sun exposure, such as exposing the backs of the hands, face, and arms for 5 to 15 minutes a day three times weekly, may be sufficient to ensure adequate levels of vitamin D.[5] Furthermore, other studies report that sun avoidance does not cause significant vitamin D deficiency.[6-8] Many individuals assume that in the absence of sun exposure, vitamin D obtained from dietary sources (either vitamin D_2, ergocalciferol, from plants; or vitamin D_3, cholecalciferol, typically from animal sources) is adequate to avoid deficiency. However, recent literature indicates that the range of "normal" values used in these sun protection studies was too low for preventing bone fractures.[9-12] Moreover, mounting evidence indicates that vitamin D may also play a role in preventing hypertension as well as certain cancers.[13-24] Therefore, the minimal acceptable levels of vitamin D need to be reassessed for the population as a whole, and particularly for individuals who are practicing sun avoidance. This paper will review the literature dealing with the need for recommending vitamin D supplementation, particularly in high-risk groups.

VITAMIN D METABOLISM AND PHYSIOLOGY

When skin is exposed to sufficient UVB (290 to 320 nm), the hormonal cascade for the endogenous production of vitamin D is activated. Through UVB radiation-mediation, the prohormone 7-dehydrocholesterol is converted into pre-vitamin D_3, which is chemically altered by the skin's temperature into cholecalciferol (calciol) or vitamin D_3.[25] Cholecalciferol is transported in the blood and is cleared from the blood by the liver, where it is converted into 25-

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TABLE 1. Dietary Reference Intake (DRI) for Various Age Groups*

Age Group	*DRI*
Children	200 IU (5 μg)
Adults <50	200 IU (5 μg)
Adults 50–70	400 IU (10 μg)
Adults >70	600-800 IU (15-20 μg)

*Sources: Yates et al[33] and Compston.[34]

hydroxycholecalciferol (25-hydroxyvitamin D, calcidiol). It is the serum level of this metabolite that is reflective of current vitamin D status. 25-Hydroxycholecalciferol (25-hydroxyvitamin D) travels to the kidneys, where it undergoes further conversion into the most active hormonal form of vitamin D, 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D, calcitriol), which enhances absorption of calcium and phosphorus from the intestine and may cause increased reabsorption of calcium in the kidneys.[26,27] This serves to elevate the plasma concentrations of calcium and phosphorus and in a feedback loop with the parathyroid glands, prevents parathyroid hormone (PTH) from increasing osteoclastic action, which would lead to the release of calcium from the bones to the serum.[5] Through these mechanisms, vitamin D sufficiency results in normal bone mineralization during development and growth in children and maintains bone strength in adults. If an individual obtaining inadequate amounts of vitamin D from dietary sources also receives insufficient levels of UVB radiation, the resulting vitamin D insufficiency is clinically manifested as rickets in children and as osteomalacia in adults.[26,28] While dietary/supplemental calcium is also important, in the absence of adequate serum vitamin D, excess calcium will simply be excreted.[29] Conversely, adequate serum vitamin D can allow the body to adapt to extremely low levels of calcium intake.[30]

VITAMIN D AND DIET: OFTEN NOT ENOUGH

The name ascribed to cholecalciferol and the related metabolites is a misnomer by having the label “vitamin” attached to “D.” Although it would more appropriately be considered a secosteroid hormone, vitamin D was discovered during the period (the late teens and early 20s of the 20th century) when “vital amines” were being discovered in foods.[31,32] The name implies “nutrient,” but it is exceptionally difficult to obtain adequate levels of vitamin D solely from the diet. The current Dietary Reference Intake (DRI) is 400 IU (or 10 μg) per day for adults over age 50, 600 IU (15 μg) for adults over age 70, and 200 IU (5 μg) for all other adults and children.[33] Some researchers recommend an even higher dose of 800 IU (20 μg) per day for older adults (Table 1).[34] Each day, one would need to eat approximately 25 to 100 g of fatty, oily fish to obtain the daily requirement of vitamin D. Eating 25 g of sardines provides between 7 and 10 μg of vitamin D; other fatty, oily fish generally provide much lower amounts.[35] Besides these fish, most other foods naturally provide little or no vitamin D (Table 2).

TABLE 2. Amounts of Vitamin D in Various Foods*

Foods Containing Vitamin D	*Vitamin D/Portion (IU)*	*(μg)*
Ready-to-eat cereal (serving)	40	1
Egg substitutes (1)	22	0.55
Real egg (1)	24	0.6
Evaporated milk (2 T)	24	0.6
Nonfat dry milk (1/3 cup)	100	2.5
Whole, fresh, fortified milk (cup)	100	2.5
Coffee cream (1 oz)	16	0.4
Butter (2 pats)	4	0.1
Cheese (100 g)	12-16	0.3-0.4
Liver		
Beef (100 g)	8	0.2
Calf (100 g)	0-12	0.0-0.3
Chicken (100 g)	48-68	1.2-1.7
Fish/Seafood		
Swordfish (100 g)	1,800	45
Sardines (100 g can)	1,160-1,560	29-39
Mackerel (100 g raw)	1,120	28
Salmon (100 g can/serving)	240-480	6-12
Salmon (100 g raw)	160-560	4-14
Herring (100 g raw or canned)	320	8
Tuna† (100 g raw)	288	7.2
Halibut (100 g)	40	1
Shrimp (100 g)	160	4
Oysters (3-4 medium-sized)	4	0.1

*Sources: Bowes A: *Bowes' and Church's Food Values of Portions Commonly Used*. Philadelphia, JB Lippincott, 1998.
Neer.[35]
Sadler M (editor-in-chief): *Encyclopedia of Human Nutrition*. New York, Academic Press, 1999.
†Tuna: canned tuna as processed in the United State removes virtually all vitamin D since this is found in the liver and tuna oils.

Because of the limited natural sources of vitamin D, the United States government chose to fortify milk to prevent rickets.[36-40] Other dairy products, such as cheese, yogurt, ice cream, and cottage cheese, are typically not fortified. As long as whole milk is drunk daily in quantity (each cup should provide at least 100 IU), this method works relatively well. However, much of the world’s populations cannot process lactose after weaning from the breast.[41-43] High rates of lactose malabsorption occur among populations in Asia and Africa, among Native Americans in North and South America, and among southern Europeans.[44] Therefore, while a goal of achieving adequate levels of vitamin D through fortification of milk may be attainable for those of northern European ancestry, even in this group few individuals actually consume the requisite amount of milk each day to meet the DRI of vitamin D. Of further concern, one group of researchers found that up to 70% of milk containers sampled had less than the stated value of vitamin D.[45-47] In addition, consumers are increasingly switching to lower fat versions of milk. In one report,[45] three of 14 skim milk containers sampled had no measurable vitamin D, while another study[48] found that up to 47% of skim milk samples contained 0% to 50% of the amount of vitamin D claimed on the label, underscoring the fact that skim milk may be an inadequate source of vitamin D.[45]

SKELETAL CONSEQUENCES OF VITAMIN D DEFICIENCY

Although it is well recognized that adequate vitamin D protects infants and children from rickets,[9,26,31,49] many clinicians may not be aware that rickets is still a problem. One illustrative case for clinicians who advocate sun avoidance was reported in 1999. A lightly-pigmented infant of European ancestry living in Toronto, Canada, had florid rickets.[50] His mother had carefully followed directions to protect her son from exposure to UVB radiation, including the use of sunscreen. However, efforts to protect him from photodamaged skin resulted in the development of a severe bone mineralization disorder.

The previously recommended adult intake of vitamin D was one half of the 10 μg or 400 IU per day that had been recommended for infants and children to prevent rickets.[9] However, recent research indicates that in addition to preventing rickets, adequate vitamin D levels are necessary to protect against osteoporosis. Many older adults, particularly those confined to nursing homes, have inadequate levels of vitamin D, and between 26 million and 38 million US adults are estimated to already have or to be at risk for osteoporosis.[51-53] Recent literature indicates that the lower acceptable limit of serum 25-hydroxyvitamin D should be a level at which PTH is suppressed so as to minimize osteoclastic action on the bones.[9] With the prevention of PTH-mediated bone loss as the foundation for recent recommendations to increase vitamin D levels, researchers have suggested the optimal level should be at least 30 ng/mL of 25-hydroxyvitamin D[11] and probably more than 40 ng/mL of 25-hydroxyvitamin D,[9] particularly for older adults.

In one prospective, placebo-controlled 3-year study of the effects of vitamin D and calcium supplementation on bone fractures in individuals over the age of 65, the average initial 25-hydroxyvitamin D values for the placebo group were 33.6 ng/mL (men) and 24.5 ng/mL (women); initial values for the treatment groups were 33.0 ng/mL (men) and 28.7 ng/mL (women). At the end of 3 years, the placebo group averaged 30.9 (men) and 25.2 ng/mL (women); the treatment group averaged 44.8 (men) and 44.8 ng/mL (women). Fractures occurred in 13% of the placebo group and only 6% of the treatment group.[12] As the US population continues to age, measures to prevent osteoporotic fractures by vitamin D supplementation, along with ensuring adequate calcium intake, will take on greater importance.

POTENTIAL EFFECTS OF VITAMIN D DEFICIENCY

Recent studies indicate that vitamin D may have important physiologic roles beyond its effects on bones. Adequate levels of vitamin D may confer resistance to tuberculosis, and individuals who receive vitamin D supplements have been shown to have an improved course of the disease.[54-56] Research has also shown that 1,25-dihydroxyvitamin D_3 restricts the growth of *Mycobacterium tuberculosis* in macrophages.[57,58] There were between 6.3 and 11.1 million new cases of TB worldwide in 1997, and between 1.4 and 2.8 million people died of TB in 1997.[58] Moreover, about 10.7 million individuals worldwide are infected with both *M tuberculosis* and human immunodeficiency virus.[59] Since approximately one third of the world's population is infected with *M tuberculosis*,[58] and since world travel is becoming increasingly common, measures that might curtail this infection, such as avoiding vitamin D deficiency, need to be a global priority.

Epidemiologic evidence shows that vitamin D plays a role in blood pressure regulation. Increased blood pressure has been shown to be associated with low 25-hydroxyvitamin D levels.[14,15,60] Another study found a relationship between latitude and blood pressure: rates of hypertension increase further from the equator.[13] A clinical report showed that patients with mild hypertension who were exposed to total body UVB radiation therapy increased their 25-hydroxyvitamin D levels and reduced their blood pressure.[14]

Analogous to the association of hypertension and latitude, epidemiologic studies have found that breast, colorectal, and prostate cancers are more prevalent in northern latitudes in the United States.[23,61] Men living in countries in Central Africa, in the Equatorial zone, have low rates of prostate cancer (4 to 10/100,000), while men who are of West or Central African ancestry and living in the United States have the world's highest rates (60 to 65/100,000).[21] The active hormonal form of vitamin D (1,25-dihydroxyvitamin D_3) has been shown to act as a tumor suppressant in breast,[16-18] colorectal,[19,20] and prostate cancers.[16,17,21-24] Prostate screenings beginning at age 40 are recommended for African-American men,[62] since prostate cancer is disproportionately aggressive at a younger average age (50 to 59) in this group than in European-American men[63]; yet, heavily pigmented African-American men are at lower risk for skin cancer because melanin acts as a natural sunscreen.[64,65]

Another cancer whose course may be attenuated by vitamin D is melanoma. Research has shown that the active hormonal form of vitamin D (1,25-dihydroxyvitamin D_3) induces cellular death in some types of melanoma. The effect is particularly strong in those cells with high levels of vitamin D receptors.[66,67] It may be that lightly-pigmented individuals with low levels of serum vitamin D are more prone to melanoma than those with high levels, and this could explain why outdoor workers continually exposed to high levels of UVB radiation tend to have lower rates of melanoma than do those whose exposure is intermittent.[1] One could postulate that those with high UVB exposure may have physiologically more protective serum levels of vitamin D compared with individuals who are only intermittently exposed.

BALANCING PUBLIC HEALTH MEASURES IN HIGH RISK GROUPS

The DRI of 200 IU/day of vitamin D for adults has been raised (1998) to 400 IU/day for adults over age 50.[33] Yet, a recent analysis of the first National Health and Nutrition Examination Survey Epidemiologic Study (NHANES I) data showed that the amount of vitamin D obtained through dietary sources averaged only 148 IU/day.[68] Analysis of a large number of studies on vitamin D supplementation concluded that individuals varied in the amount of vitamin D supplementation and/or UVB radiation exposure they required to reach a specific level of serum 25-hydroxyvitamin D. Therefore, while the current DRI of vitamin D may be adequate for some individuals, it is probably inadequate for others.[9] Particularly because of the high incidence of bone fractures in the elderly, it has been suggested that the appropriate amount should exceed 1,000 IU/ day,[9] since even an intake of 2,000 IU/day is still below the level that is associated with hypervitaminosis D and hypercalcemia in individuals over 1 year of age.[33] However, increasing vitamin D to levels significantly above the DRI should be viewed with caution because of a tendency among some individuals to have kidney stones.[69]

Since purely dietary means of achieving adequate vitamin D are difficult, it would be tempting to recommend a public health policy of having individuals get vitamin D by going out in the sun when there is significant UVB radiation, especially since this method more closely correlates with 25-hydroxyvitamin D levels than does dietary supplementation.[9,53] However, this directly contradicts measures advocated to prevent skin cancer.

Conversely, in attempting to promote skin cancer prevention, we must be careful not to exacerbate vitamin D deficiency. This is particularly of concern in heavily pigmented populations living in northern latitudes and at low risk for skin cancer, but at greatest risk for vitamin D deficiency, since dark-skinned individuals may require up to six times the exposure to UVB radiation required by light-skinned individuals to maintain adequate levels of serum vitamin D,[9,70] by virtue of melanin acting as an extremely effective sunblock.[64,65]

Sunscreen blocks solar UVB radiation (290 to 320 nm), thereby preventing sunburn and cutaneous carcinogenesis, but it also impairs the synthesis of vitamin D.[71,72] Two reports studied the effects of sunscreen and vitamin D synthesis in healthy subjects.[6,7] In an Australian study, individuals who wore sunscreen had an average level of 25-hydroxyvitamin D of 27.3 ng/mL, whereas the control subjects using placebo had levels of 25-hydroxyvitamin D of 25.7 ng/mL.[7] In a Spanish study, basal levels of 25-hydroxyvitamin D in the controls averaged 22.5 ng/mL, while the sunscreen users averaged 19.9 ng/mL. After months of sun exposure, the highest 25-hydroxyvitamin D levels measured in this study averaged 34.8 ng/mL for the control group and 26.8 ng/mL for the sunscreen group.[6] Also, a study of individuals with xeroderma pigmentosum (who are genetically predisposed to having numerous skin cancers before adulthood, and consequently are motivated to practice strict sun protection) failed to show vitamin D deficiency in any of the subjects studied.[8] These three papers concluded that there is no significant effect of sunscreen use on vitamin D levels.

However, if the value of 40 ng/mL of 25-hydroxyvitamin D considered desirable to prevent osteoporotic fractures is used for the lower limit, none of the patients analyzed during the course of the xeroderma pigmentosum study had adequate levels of 25-hydroxyvitamin D,[8] nor were the average levels adequate in the sunscreen studies done in Spain[6] and Australia.[7] While the mean values of 25-hydroxyvitamin D for non–sunscreen-wearing controls were below newly recommended minimum values, those who wore sunscreen were even more deficient. Since Australia receives more UVB radiation than does most of the continental United States, and since the participants in the sunscreen studies were of European ancestry, and presumably not heavily pigmented, vitamin D supplementation needs to be considered for those who practice skin cancer prevention and who are at greatest risk of diminished cutaneous production. Those individuals who assiduously avoid the midday sun, wear protective clothing, regularly use sunscreen, and/or have dark skin would be at greatest risk of having vitamin D deficiency unless adequately supplemented.

Avoidance of vitamin D deficiency is especially important during breastfeeding, since breastfed infants who do not receive vitamin D supplementation are reliant on their mothers' stores of vitamin D and their own cutaneous synthesis of vitamin D. Therefore, it is crucial for a breastfeeding mother who practices sun avoidance to ensure that both she and her infant obtain adequate vitamin D supplementation.[73,74]

Evidence is accumulating that beyond its effects on skeletal health, vitamin D may ameliorate the course of tuberculosis and hypertension; and may act as a tumor-suppressant in cancers of the breast, colon, and prostate, and possibly malignant melanoma. In view of recent guidelines aiming to prevent osteoporosis, the majority of Americans may be vitamin D deficient.[9,68] Individuals who are getting only small amounts of UVB radiation appear to be at highest risk. However, in an effort to prevent skin cancers, sun avoidance beginning at an early age is also a major public health priority. Conflicting public health recommendations need to be balanced against each other, since overzealous sun protection may potentially have a serious downside.

In those settings in which patients are being counseled regarding sun protection, a discussion of vitamin D intake should be provided, which for most patients will probably involve more than drinking milk. Only if the cost or accessibility of supplementation is prohibitive should increased sun exposure be advised. This needs to be done extremely carefully, since the risk of developing skin cancer would have to be balanced against the risk of inadequate vitamin D intake. Such a recommendation should only follow an extensive consideration of the risk/benefit ratio to the individual of having skin cancer compared with the effects of vitamin D deficiency.

In summary, if we fail to consider the need for vitamin D supplementation, particularly in individuals who are practicing sun protection, physicians may inadvertently foster an upsurge in vitamin D deprivation with associated systemic health problems. As the importance of vitamin D becomes further elucidated, increasingly greater emphasis will be placed on adequate vitamin D supplementation, which for older individuals is currently two to four times the amount recommended just a few years ago. Increasing attention needs to be placed on measuring 25-hydroxyvitamin D and on advocating vitamin D supplementation along with sun avoidance. Such a policy will allow individuals to improve the health of their skin and bones, and possibly much more.

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