Vitamin D deficiency: a worldwide problem with health consequences\textsuperscript{1–4}

Michael F Holick and Tai C Chen

ABSTRACT
Vitamin D deficiency is now recognized as a pandemic. The major cause of vitamin D deficiency is the lack of appreciation that sun exposure in moderation is the major source of vitamin D for most humans. Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child’s or an adult’s vitamin D requirement. Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults. Vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases. A circulating level of 25-hydroxyvitamin D of \( \geq 75 \text{ nmol/L} \) or \( \geq 30 \text{ ng/mL} \) is required to maximize vitamin D’s beneficial effects for health. In the absence of adequate sun exposure, at least \( 800–1000 \text{ IU} \) vitamin \( D_2/d \) may be needed to achieve this in children and adults. Vitamin \( D_2 \) may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations. \textit{Am J Clin Nutr} 2008;87(suppl):1080S–6S.

HISTORICAL PERSPECTIVE
Some of the earliest phytoplankton life forms on earth that have existed unchanged in the Atlantic ocean for \( \geq 750 \text{ y} \) can make vitamin D when exposed to sunlight (1, 2). Most vertebrates, including amphibians, reptiles, birds, and lower primates, depend on sun exposure for their vitamin D requirement (2). The lack of sunlight and its association with the devastating bone-deforming disease rickets in children was first recognized by Sniaidecki in 1822 (3). One hundred years would pass before it was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented. Sniadecki in 1822 (3). One hundred years would pass before it was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented and was observed that exposure to ultraviolet B radiation (UVB; 290–315 nm) from a mercury arc lamp or sunlight prevented. The major source of vitamin D for most humans is exposure to sunlight (1, 2). As shown in Figure 1, seasonal variation is found in the major circulating form of vitamin D, 25-hydroxyvitamin D [25(OH)D] (8). Few foods naturally contain vitamin D, including oily fish such as salmon, mackerel, and herring and oils from fish, including cod liver oil. We recently conducted a study and observed that wild-caught salmon had on average 500–1000 IU vitamin D in 100 g (3.5 ounces), whereas farmed salmon contained \( \approx 100–250 \text{ IU} \) vitamin D per 100-g serving (9). The most likely reason is that vitamin D is plentiful in the food chain but is not plentiful in the pelleted diet fed to farmed salmon. In the United States, milk, some juice products, some breads, yogurts, and cheeses are fortified with vitamin D. Multivitamins that contain 400 IU vitamin D and supplements containing vitamin D only are now available in various amounts including 400, 1000, 2000, 4000, 5000 and 50,000 IU vitamin D. The pharmaceutical form of vitamin D in the United States is vitamin D\(_2\) and is available as 50,000 IU vitamin D\(_2\) in a capsule or 8000 IU vitamin D\(_3\)/mL (4, 10). In Canada, Europe, Japan, and India, vitamin D\(_3\) is available as a pharmaceutical.

CONSEQUENCES OF VITAMIN D DEFICIENCY ON THE MUSCULOSKELETAL SYSTEM
Much debate has taken place over the definition of vitamin D deficiency. Most agree that a 25(OH)D concentration <50 nmol/L, or 20 ng/mL, is an indication of vitamin D deficiency, whereas a 25(OH)D concentration of 51–74 nmol/L, or 21–29 ng/mL, is considered to indicate insufficiency; concentrations

---

\textsuperscript{1} From the Department of Medicine; Section of Endocrinology, Nutrition, and Diabetes; Vitamin D, Skin and Bone Research Laboratory; Boston University Medical Center, Boston, MA.

\textsuperscript{2} Presented at the symposium “Assessment of Vitamin D in Population-Based Studies,” held at Experimental Biology 2007 in Washington, DC, 1 May 2007.

\textsuperscript{3} Supported in part by NIH grant M01RR00533 and by the UV Foundation.

\textsuperscript{4} Reprints not available. Address correspondence to MF Holick, Boston University School of Medicine, 715 Albany Street, M-1013, Boston, MA 02118. E-mail: mfholick@bu.edu.
>30 ng/mL are considered to be sufficient (10–15; Figure 2) This is based on the observation that intestinal calcium absorption is maximized above 80 nmol/L, or 32 ng/mL, in postmenopausal women (16) and that parathyroid hormone (PTH) concentrations in adults continue to decline and reach their nadir at ≈75–100 nmol/L, or 30–40 ng/mL (11, 14, 15). It has been assumed that children have the same requirement as adults; however, no comparable studies have been carried out on intestinal calcium transport or PTH levels in children. Vitamin D intoxication typically does not occur until 25(OH)D concentrations are >375 nmol/L, or 150 ng/mL (10, 16, 17).

Vitamin D deficiency in children will cause growth retardation (5, 18) and classic signs and symptoms of rickets (4–6, 18). In adults, vitamin D deficiency will precipitate and exacerbate both osteopenia and osteoporosis and increase the risk of fracture (10, 11, 19, 20).

Muscle weakness has long been associated with vitamin D deficiency. A vitamin D receptor is present in skeletal muscle (21), and vitamin D deficiency has been associated with proximal muscle weakness, increase in body sway, and an increased risk of falling (22–24).

Vitamin D deficiency in adults can also cause a skeletal mineralization defect. The unmineralized osteoid provides little structural support for the periosteal covering. As a result, patients with osteomalacia often complain of isolated or global bone discomfort along with aches and pains in their joints and muscles (25–27). These patients may be misdiagnosed with fibromyalgia, dysthymia, degenerative joint disease, arthritis, chronic fatigue syndrome, and other diseases (10, 25, 28).

CAUSES OF VITAMIN D DEFICIENCY
The major source of vitamin D for humans is exposure to sunlight (4, 8, 10). Anything that diminishes the transmission of solar UVB radiation to the earth’s surface or anything that interferes with the penetration of UVB radiation into the skin will affect the cutaneous synthesis of vitamin D3 (2, 9; Figure 3) Melanin is extremely efficient in absorbing UVB radiation, and,
7-dehydrocholesterol, the precursor of vitamin D3 in the skin. A lack of vitamin D deficiency (33–42). This includes both children and adults living in the United States, Europe, Middle East, India, Australia, and Asia. These studies suggest that upwards of 30–50% of children and adults are at risk of vitamin D deficiency and explains why in the sunniest areas of the world vitamin D deficiency is very common in both children and adults (33, 34). No one is immune from vitamin D deficiency. Thus, increased skin pigmentation markedly reduces vitamin D3 synthesis (29). Similarly, a sunscreen with a sun protection of 15 absorbs 99% of the incident UVB radiation, and, thus, when topically applied properly will decrease the synthesis of vitamin D3 in the skin by 99% (30). African Americans with very dark skin have an SPF of 15, and, thus, their ability to make vitamin D in their skin is reduced by as much as 99% (9, 29). This along with decreased milk intake are the explanations for why most African Americans who live in a temperate climate are vitamin D deficient, whereas Africans living near the equator where vitamin D3 synthesis is more efficient because of the higher flux of UVB photons are not (31, 32).

The angle at which the sun reaches the earth has a dramatic effect on the number of UVB photons that reach the earth’s surface (2, 31). This is why when the zenith angle is increased during the wintertime and in the early morning and late afternoon, little if any vitamin D3 synthesis occurs (2, 31). The practice of purdah, whereby all skin is covered and prevented from being exposed to sunlight places those who practice it at high risk of vitamin D deficiency and explains why in the sunniest areas of the world vitamin D deficiency is very common in both children and adults (33, 34). No one is immune from vitamin D deficiency. This includes both children and adults living in the United States, Europe, Middle East, India, Australia, and Asia. These studies suggest that upwards of 30–50% of children and adults are at risk of vitamin D deficiency (33–42).

Aging is associated with decreased concentrations of 7-dehydrocholesterol, the precursor of vitamin D3 in the skin. A 70-y-old has ≈25% of the 7-dehydrocholesterol that a young adult does and thus has a 75% reduced capacity to make vitamin D3 in the skin (43). Because vitamin D is fat soluble, it is readily taken up by fat cells. Obesity is associated with vitamin D deficiency, and it is believed to be due to the sequestration of vitamin D by the large body fat pool (44). Medications including anti-seizure medications and glucocorticoids and fat malabsorption are also common causes of deficiency (45; Figure 3).

Thus, vitamin D deficiency is not uncommon. The majority of people are vitamin D-deficient, but the severity of the deficiency is often not recognized. Vitamin D deficiency is considered to be a public health problem, and efforts are needed to prevent and treat vitamin D deficiency, especially in high-risk groups such as African Americans (33), breast-fed infants (40), and elderly people (41). The WHO has recently released guidelines on vitamin D deficiency, which recommend that all pregnant women should receive at least 400 IU vitamin D per day to ensure that their infants have adequate vitamin D status (35).

**VITAMIN D DEFICIENCY CONSEQUENCES**

**CANCER**
- Breast
- Colon
- Prostate
- Pancreatic

**INFECTIONS**
- UTI
- TB
- URI
- Rheumatic fever

**SKELETAL CONSEQUENCES**
- Osteomalacia
- Rickets

**NONSERIAL CONSEQUENCES**

**MECHANISMS OF ACTION OF VITAMIN D**

Vitamin D is metabolized in the liver to 25(OH)D and then in the kidneys to 1,25(OH)2D (70, 71; Figure 2). It is also recognized that many other tissues in the body, including...
Macrophages, brain, colon, prostate, breast, and others, have the enzymatic machinery to locally produce 1,25(OH)2D (72–76; Figure 4). 1,25(OH)2D produced by the kidneys enters the circulation and travels to its major target tissues the intestine and bone, where it interacts with its vitamin D receptor to enhance intestinal calcium absorption and mobilize osteoclasts, which has been reported to be only 30% to 50% as effective as vitamin D3. This study evaluated vitamin D2, which has been reported to be only 30% to 50% as effective as vitamin D3 in maintaining serum 25(OH)D concentrations (93, 94). Our data suggest that vitamin D2 was effective in raising blood concentrations of 25(OH)D by ≥1 ng/100 IU, as has been reported for vitamin D3 (91, 95). These data are consistent with our recent observation that 1000 IU vitamin D2/d was as effective as 1000 IU vitamin D3/d in raising and maintaining serum 25(OH)D concentrations (91). Thus, physiologic doses of vitamin D2 may be equally effective as vitamin D3 in maintaining serum 25(OH)D concentrations.

To treat vitamin D deficiency in the United States, 50 000 IU vitamin D2 (or vitamin D3, which is available in Canada, Europe, Japan, and India) once a week for 8 wk often attains a 25(OH)D concentration of ≈75 nmol/L (13). To maintain vitamin D sufficiency, Holick (10) recommends that 50 000 IU vitamin D2 to the age of 50 y require 200 IU vitamin D/d and adults aged 51–70 and ≥71 y need 400 and 600 IU vitamin D/d (83). The National Osteoporosis Foundation recently recommended that all postmenopausal women take 800–1000 IU vitamin D/d (84). Cheng et al (85) reported an association of low 25(OH)D concentrations with elevated serum PTH concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. This confirmed the earlier observations of Outila et al (86), who noted elevated PTH concentrations and lower forearm bone density and vitamin D deficiency in the winter in adolescent females, and Guilemanc et al (87), who observed seasonal variation in PTH concentrations in growing male adolescents. When 171 prepubertal girls were given 400 IU vitamin D2/d from October to February and 500 mg Ca supplementation, their serum 25(OH)D concentrations did not change. When these girls received 800 IU vitamin D2/d, their blood concentrations rose during the winter but did not reach concentrations observed during the summer (88). Thus, on the basis of these and other observations, many experts now agree that in the absence of adequate sun exposure, 800–1000 IU vitamin D/d is needed for children of all ages and adults of all ages (84, 88–91), although this is not the current recommendation of pediatric or governmental organizations. Higher doses may be required if fat malabsorption, obesity, or other causes exist that would enhance vitamin D catabolism and its destruction (10, 45; Figure 2). As many as 4 different enzymes have been suggested to be capable of converting vitamin D to 25(OH)D (92). These enzymes most likely have different K\textsubscript{m} values for vitamin D and have different levels of negative feedback regulation by the serum 25(OH)D concentration. Thus, circulating 25(OH)D concentrations in response to vitamin D may be influenced by the baseline 25(OH)D concentration. As can be seen in Figure 5, the baseline concentration of 25(OH)D is an important factor for how a person responds to a vitamin D dose. When serum 25(OH)D concentrations were <50 nmol/L (20 ng/mL) in nursing home patients, doses of 200, 400, and 600 IU vitamin D2/d for 5 mo (23) raised serum 25(OH)D concentrations by ≈100% to ≈62 nmol/L (24 ng/mL). Only when the dose was increased to 800 IU/d for 5 mo did concentrations rise above 75 nmol/L, or 30 ng/mL (Figure 5). However, subjects who had starting mean 25(OH)D concentrations above 64 nmol/L (25 ng/mL) showed no significant change in their serum 25(OH)D concentrations when they took 200, 400, 600, or 800 IU/d. When the baseline 25(OH)D concentration was above 50 nmol/L (20 ng/mL), only 800 IU vitamin D2/d for 5 mo was effective in raising the serum 25(OH)D level (Figure 5). This study evaluated vitamin D2, which has been reported to be only 30% to 50% as effective as vitamin D3 in maintaining serum 25(OH)D concentrations (93, 94). Our data suggest that vitamin D2 was effective in raising blood concentrations of 25(OH)D by ≥1 ng/100 IU, as has been reported for vitamin D3 (91, 95). These data are consistent with our recent observation that 1000 IU vitamin D2/d was as effective as 1000 IU vitamin D3/d in raising and maintaining serum 25(OH)D concentrations (91). Thus, physiologic doses of vitamin D2 may be equally effective as vitamin D3 in maintaining serum 25(OH)D concentrations.

FIGURE 4. Metabolism of 25-hydroxyvitamin D (25(OH)D) to 1,25-dihydroxyvitamin D [1,25(OH)\textsubscript{2}D] for nonskeletal functions. When a monocyte or macrophage is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infective agent such as Mycobacterium tuberculosis (TB) or its lipopolysaccharide (LPS), the signal up-regulates the expression of vitamin D receptor (VDR) and the 25-hydroxyvitamin D-1-hydroxylase (1-OHase). 1,25(OH)\textsubscript{2}D increases the expression of cathelicidin (CD). When 25(OH)D concentrations are ≈30 ng/mL, the risk of many common cancers is reduced. It is believed that the local production of 1,25(OH)\textsubscript{2}D regulates genes that control proliferation and apoptosis. AB, B-lymphocytes; AT, T-lymphocytes; BP, blood pressure; BS, blood sugar; 24-OHase, 25-hydroxyvitamin D-24-hydroxylase; PTH, parathyroid hormone.
This, however, did not mean that vitamin D2 was less active than vitamin D3 in maintaining serum concentrations of 25(OH)D (93, 94).

Vitamin D3 in maintaining serum concentrations of 25(OH)D (93, 94).

The best method for determining a person’s vitamin D status is to measure a 25(OH)D concentration. Most commercial assays are reliable enough to determine a person’s vitamin D status (10).

The literature over the past decade suggests that the Institute of Medicine recommendations in 1997 (83) are inadequate, and some experts including us suggest that both children and adults should take ≥800–1000 IU vitamin D/d from dietary and supplemental sources (4, 9, 77) when sunlight is unable to provide it. This recommendation, however, has not yet been embraced either by official government or pediatric organizations in the United States, Canada, or Europe for either children or adults.

Neither of the authors had a conflict of interest.

REFERENCES

8. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption and serum 25-hydroxyvitamin D in nursing home residents with initial 25(OH)D serum concentrations of either <20 ng/mL (△ △) or ≥20 ng/mL ( ) before and after receiving 0, 200, 400, 600, or 800IU vitamin D2/d for 5 mo from October through March. Data are from 6–16 individuals. *P < 0.05; **P < 0.01; ***P < 0.001.

FIGURE 5. Mean (±SE) circulating concentrations (A) and changes (B) in 25-hydroxyvitamin D [25(OH)D] in nursing home residents with initial 25(OH)D serum concentrations of either <20 ng/mL (△ △) or ≥20 ng/mL ( ) before and after receiving 0, 200, 400, 600, or 800IU vitamin D2/d for 5 mo from October through March. Data are from 6–16 individuals. *P < 0.05; **P < 0.01; ***P < 0.001.

CONCLUSION

Throughout evolution, humans have depended on the sun for their vitamin D requirement (1, 2). Indeed, a likely reason that melanin pigmentation devolved was to permit humans who migrated north and south of the equator to make enough vitamin D in their skin to satisfy their requirement (96). The recommendation for the avoidance of all sun exposure has put the world’s population at risk of vitamin D deficiency (97). This has become apparent in Australia, where a dramatic increase in skin cancer rates resulted in the promotion of never exposing the skin to direct sunlight without sun protection, ie, clothing or sunscreen. The so-called sun-safe message has resulted in a marked increase in the risk of vitamin deficiency in Australia (40).

The best method for determining a person’s vitamin D status is to measure a 25(OH)D concentration. Most commercial assays are reliable enough to determine a person’s vitamin D status (10). These include various radioimmunoassays (98) and what is now considered to be the gold standard: liquid chromatography–tandem mass spectrometry (14). There has been much discussion about vitamin D2 being only ≈30–50% as effective as vitamin D3 in maintaining serum concentrations of 25(OH)D (93, 94). This, however, did not mean that vitamin D2 was less active than vitamin D3 once it was metabolized to 1,25(OH)2D2. It only meant that vitamin D2 may need to be given in higher doses to raise the blood concentrations of 25(OH)D above 75 nmol/L, or 30 ng/mL. Our data (Figure 5), as well as our recent observation that vitamin D2 was as effective as vitamin D3 in raising the blood concentrations of 25(OH)D (91), however, calls into question whether this is really necessary.

A reevaluation needs to take place of what the adequate intakes of vitamin D should be for children and adults. The literature over the past decade suggests that the Institute of Medicine recommendations in 1997 (83) are inadequate, and some experts including us suggest that both children and adults should take ≥800–1000 IU vitamin D/d from dietary and supplemental sources (4, 9, 77) when sunlight is unable to provide it. This recommendation, however, has not yet been embraced either by official government or pediatric organizations in the United States, Canada, or Europe for either children or adults.

Neither of the authors had a conflict of interest.

REFERENCES

20. Larsen ER, Moskilde L, Foldspang A. Vitamin D and calcium supple-
mentation prevents osteoporotic fractures in elderly community dwell-

21. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-

dihydroxyvitamin D concentrations are associated with better lower-
extremity function in both active and inactive persons aged ≥60 y. Am J Clin Nutr 2004;80:752–8.


30. Matsouka LY, Ide L, Wortsman J, MaLaughlin JA, Holick MF. Sun-


34. Visser M, Meeg DHJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength among an elderly mass (sarcopenia): the longitudinal aging study Amsterdam. J Clin Endocrinol Metab 2003;88:5766–72.


54. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Fin-


59. Embry AF, Snowdon CR, Vieth R, Vitamin D and seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in mul-

60. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension 1979;30:150–6.


62. Mungur KL, Zhang SM, O’Reilly E, et al. Vitamin D intake and inci-

63. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis. Arth-

64. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ul-

65. McGrath J, Selten JP, Chant D. Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first regis-

66. Gloth FM III, Alam W, Hollis B. Vitamin D vs. broad spectrum photo-

83. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 2007 Dec 18 [Epub ahead of print].