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

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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 >75 nmol/L, or 30 ng/mL, is required to maximize vitamin D’s beneficial effects for health. In the absence of adequate sun exposure, at least 800–1000 IU vitamin D\textsubscript{2}/d may be needed to achieve this in children and adults. Vitamin D\textsubscript{2} may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations.

HISTORICAL PERSPECTIVE
Some of the earliest phytoplankton life forms on earth that have existed unchanged in the Atlantic ocean for >750 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 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 treated rickets (4). In the early 1930s, the US government set up an agency to provide recommendations to parents about the beneficial effect of sensible exposure to sunlight for the prevention of rickets (4–6).

The fortification of milk in the 1930s with 100 IU vitamin D\textsubscript{2} per 8 ounces was effective in eradicating rickets in the United States and Europe. The unfortunate outbreak of hypercalcemia in infants in the 1950s resulted in Europe forbidding the fortification of dairy products with vitamin D. Only recently have Finland and Sweden begun fortifying milk with vitamin D.

SOURCES OF VITAMIN D
The major source of vitamin D for most humans is exposure to sunlight (1, 2, 4–6). 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 an average 500–1000 IU vitamin D in 100 g (3.5 ounces), whereas farmed salmon contained \approx100–250 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\textsubscript{2}. The pharmaceutical form of vitamin D in the United States is vitamin D\textsubscript{2} and is available as 50 000 IU vitamin D\textsubscript{2} in a capsule or 8000 IU vitamin D\textsubscript{2}/mL (4, 10). In Canada, Europe, Japan, and India, vitamin D\textsubscript{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

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>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 substantial percentage of vitamin D deficiency (33–42).

In Europe, Middle East, India, Australia, and Asia, these studies indicate that both children and adults living in the United States, Europe, Middle East, India, Australia, and Asia are at risk of vitamin D deficiency. No one is immune from vitamin D deficiency. This includes both children and adults (33, 34). No one is immune from vitamin D deficiency.

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). 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).

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 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).

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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).

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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).

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)\(_2\)D to 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)\(_2\)D increases the expression of cathelicidin (CD). When 25(OH)D concentrations are \(\approx\) 30 nmol/L, the risk of many common cancers is reduced. It is believed that the local production of 1,25(OH)\(_2\)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.

**PREVENTION AND TREATMENT OF VITAMIN D DEFICIENCY**

The Institute of Medicine recommended that all children (also endorsed by the American Academy of Pediatrics) and adults up to the age of 50 y require 200 IU vitamin D/d and adults aged 51–70 and \(\geq 71\) 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 Guillemant et al (87), who observed seasonal variation in PTH concentrations in growing male adolescents. When 171 prepubertal girls were given 400 IU vitamin D\(_2\)/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 D\(_2\)/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 \(K_m\) 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 \(\leq 50\) nmol/L (20 ng/mL) in nursing home patients, doses of 200, 400, and 600 IU vitamin D\(_2\)/d for 5 mo (23) raised serum 25(OH)D concentrations by \(\approx 100\)% to \(\approx 62\) 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 D\(_2\)/d for 5 mo was effective in raising the serum 25(OH)D level (Figure 5). This study evaluated vitamin D\(_2\), which has been reported to be only 30% to 50% as effective as vitamin D\(_3\) in maintaining serum 25(OH)D concentrations (93, 94). Our data suggest that vitamin D\(_2\) was effective in raising blood concentrations of 25(OH)D by \(\geq 1\) ng/100 IU, as has been reported for vitamin D\(_3\) (91, 95). These data are consistent with our recent observation that 1000 IU vitamin D\(_2\)/d was as effective as 1000 IU vitamin D\(_3\)/d in raising and maintaining serum 25(OH)D concentrations (91). Thus, physiologic doses of vitamin D\(_2\) may be equally effective as vitamin D\(_3\) in maintaining serum 25(OH)D concentrations.

To treat vitamin D deficiency in the United States, 50 000 IU vitamin D\(_2\) (or vitamin D\(_3\), which is available in Canada, Europe, Japan, and India) once a week for 8 wk often attains a 25(OH)D concentration of \(\approx 75\) nmol/L (13). To maintain vitamin D sufficiency, Holick (10) recommends that 50 000 IU vitamin D\(_2\),...
This, however, did not mean that vitamin D2 was less active than vitamin D3; 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.

CONCLUSION

Throughout evolution, humans have depended on the sun for their vitamin D requirement (1, 2). Indeed, a likely reason that melanin pigmentation evolved 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 D 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 called mass spectroscopy (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)2D. 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.

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REFERENCES

20. Larsen ER, Moskilde L, Foldspang A. Vitamin D and calcium supple-
mentation prevents osteoporotic fractures in elderly community dwell-
ing residents: a pragmatic population-based 3-year intervention study.
21. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-
dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem
dihydroxy-vitamin D concentrations are associated with better lower-
extremity function in both active and inactive persons aged ≥60 y. Am J
23. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel
D. A higher dose of vitamin D reduces the risk of falls in nursing home
24. Visser M, Deeg DHJ, Lips P. Low vitamin D and high parathyroid
hormone levels as determinants of loss of muscle strength as muscle
mass (sarcopenia): the longitudinal aging study Amsterdam. J Clin En-
25. Malabanan AO, Turner AK, Holick MF. Severe generalized bone pain
and osteoporosis in a premenopausal black female: effect of vitamin D
and osteoporosis in fractures of the proximal femur. Lancet 1974;1:
326–33.
27. Al-Ali H, Fuleihan GEH. Nutritional osteomalacia: substantial clinical
improvement and gain in bone density post therapy. J Clin Densitom
28. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in
patients with persistent, nonspecific muscularkeletal pain. Mayo Clin
Proc 2003;78:1463–70.
29. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin
pigment reduces the capacity of skin to synthesize vitamin D3. Lancet
30. Matsuoka LY, Ide L, Wortsman J, MaLlughlin JA, Holick MF. Sun-
screens suppress cutaneous vitamin D3 synthesis. J Clin Endocrinol
Metab 1987;64:1165–8.
31. Webb AR, Kline L, Holick MF. Influence of season and latitude on the
cutaneous synthesis of vitamin D3; exposure to winter sunlight in Boston
and Edmonton will not promote vitamin D3 synthesis in human skin.
32. Thacher TD, Fischer PR, Strand MA, Pettifor JM. Nutritional rickets
around the world: causes and future directions. Ann Trop Paediatr 2006;
26:1–16.
33. Sedrani SH. Low 25-hydroxyvitamin D and normal serum calcium con-
centrations in Saudi Arabia: Riyadh region. Ann Nutr Metab 1984;26:
659–62.
34. Gordon CM, DePetter KC, Estherann G, Emans SJ. Prevalence of vitamin
D deficiency among healthy adolescents. Arch Pediatr Adolesc Med
35. Tangpricha V, Pearce EN, Chen TC, Holick MF, Kiel D. Diabe-
tetes prevents osteoporotic fractures in elderly community dwell-
ers: a pragmatic population-based 3-year intervention study. J Bone
91. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D$_2$ is as effective as vitamin D$_3$ in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 2007 Dec 18 [Epub ahead of print].