Vitamin D deficiency: a worldwide problem with health consequences1–4

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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 D3/d may be needed to achieve this in children and adults. Vitamin D2 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, 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 on average 500–1000 IU vitamin D in 100 g (3.5 ounces), whereas farmed salmon contained ≈100–250 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 D3. The pharmaceutical form of vitamin D in the United States is vitamin D2 and is available as 50 000 IU vitamin D2 in a capsule or 8000 IU vitamin D3/mL (4, 10). In Canada, Europe, Japan, and India, vitamin D3 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,

FIGURE 1. A: Relation between hours of sunshine and serum 25-hydroxyvitamin D [25(OH)D] concentrations. ■, hours of sunshine; ●, 25(OH)D. B: Seasonal fluctuation in serum 25(OH)D according to frequency of sun exposure. ■, regular sun exposure; ●, occasional sun exposure; ●, avoiding direct sun exposure. Adapted from reference 8.

FIGURE 2. Schematic representation of the synthesis and metabolism of vitamin D for regulating calcium, phosphorus, and bone metabolism. During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D₃ (preD₃) and then by a heat-dependent process to vitamin D₃. Vitamin D (D represents D₂ or D₃) made in the skin or ingested in the diet is converted by the vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D [25(OH)D]. 25(OH)D is converted in the kidneys by the 25-hydroxyvitamin D-1-hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D [1,25(OH)₂D]. 1,25(OH)₂D increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)₂D and 25(OH)D to the water-soluble biologically inactive calcitroic acid. 1,25(OH)₂D enhances intestinal calcium absorption in the small intestine. 1,25(OH)₂D is recognized by its receptor in osteoblasts, causing an increase in the expression of receptor activator of NFkB ligand (RANKL). CaBP, calcium binding protein; ECaC, epithelial channel calcium; FGF23, fibroblast growth factor 23; OJ, orange juice; Pi, inorganic phosphate; PTH, parathyroid hormone; UVB, ultraviolet B radiation.
thus, increased skin pigmentation markedly reduces vitamin D$_3$ 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 D$_3$ 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 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 D$_3$ 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 D$_3$ 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 D$_3$ 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 antiseizure medications and glucocorticoids and fat malabsorption are also common causes of deficiency (45; Figure 3).

FIGURE 3. A schematic representation of the major causes of vitamin D deficiency and potential health consequences. AODM, adult onset diabetes mellitus; CHD, coronary heart disease; FEV$_1$, forced expiratory volume in 1 s; HAART, highly active antiretroviral therapy; HBP, high blood pressure; MS, multiple sclerosis; RA, rheumatoid arthritis; TB, tuberculosis; URI, urinary tract infection.

NONSKELETAL CONSEQUENCES OF VITAMIN D DEFICIENCY

More than 80 y ago, it was reported that living at higher latitudes in the United States correlated with an increased risk of dying of common cancers (46). In the 1980s and 1990s, several observations suggested that living at higher latitudes increased the risk of developing and dying of colon, prostate, breast, and several other cancers (47–52). Because living at higher latitudes diminishes vitamin D$_3$ production, it was suggested that an association may exist between vitamin D deficiency and cancer mortality. Both men and women exposed to the most sunlight throughout their lives were less likely to die of cancer (50–54).

Several retrospective and prospective studies that evaluated circulating concentrations of 25(OH)D support the concept that vitamin D deficiency increases the risk of developing and dying from cancer (52, 53). It has been suggested that adults with 25(OH)D of <50 nmol/L who were then followed for up to 19 y had a 30–50% increased risk of developing colorectal, breast, prostate, and many other cancers (50, 52, 54, 55). A meta-analysis showed that increasing intake of vitamin D to 1000 IU vitamin D$_3$/d would be associated with a decreased risk of colorectal and breast cancer of as much as 50% (53). Men who ingested >400 IU vitamin D/d had a markedly reduced risk of developing several cancers, including those of the pancreas and esophagus and non-Hodgkin lymphoma (52). Lappe et al (56) reported that postmenopausal women who received 1100 IU vitamin D$_3$ and 1000 mg Ca daily for 4 y reduced their risk of developing cancer by 60%.

Living at higher latitudes is associated with an increased risk of type 1 diabetes (57), multiple sclerosis (58, 59), and hypertension (60). Children who received 2000 IU vitamin D/d during the first year of life and who were followed for 31 y were found to have a reduced risk of developing type 1 diabetes by 78% compared with children who were not supplemented with vitamin D (61). Women who received >400 IU vitamin D/d were found to have a >40% reduced risk of developing multiple sclerosis (62) and rheumatoid arthritis (63). Hypertensive patients who were exposed to a tanning bed raised their blood concentrations of 25(OH)D by >180% in 3 mo and became normotensive (64). Patients who live at higher latitudes and are at risk of vitamin D deficiency are also more prone to developing schizophrenia (65), and vitamin D deficiency has been associated with depression (66). Vitamin D deficiency in pregnancy has also been associated with an increased risk of preeclampsia (67).

African Americans are at higher risk of developing and having more severe cases of tuberculosis. It has been known for >100 y that exposure to sunlight helped in the treatment of tuberculosis (68). Liu et al (69) reported that the likely mechanism is that when a macrophage is infected with tuberculosis, it stimulates the cell to increase the production of 1,25-dihydroxyvitamin D$_3$ [1,25(OH)$_2$D$_3$] and increase the expression of the vitamin D receptor. In combination, they enhanced the gene expression of the bacteriocidal protein cathelicidin, which is known to kill tuberculosis and other infective agents (Figure 4).

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)$_2$D$_3$ (70, 71; Figure 2). It is also recognized that many other tissues in the body, including
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 Guillemant 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 \( K_m \) 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 \( \approx 100\% \) 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 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 \( \geq 1 \) 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 \( \approx 75 \) nmol/L (13). To maintain vitamin D sufficiency, Holick (10) recommends that 50 000 IU vitamin D2...
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.

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