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{2/3} 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, 4–6). As shown in Figure 1, seasonal variation is found in the major circulating form of vitamin D, 25-hydroxyvitamin D [25(OH)\textsubscript{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 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{3} 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,

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7-dehydrocholesterol, the precursor of vitamin D3 in the skin. A number of vitamin D deficiency (33–42). It is well recognized that many other tissues in the body, 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 D3 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 D3 [1,25(OH)2D3] 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)2D (70, 71; Figure 2). It is also recognized that many other tissues in the body, including
It is believed that the local production of 1,25(OH)2D regulates genes that are responsible for decreasing the risk of the cells being transformed into a malignant state (77). 1,25(OH)2D, which has been reported to be only 30% to 50% as effective as vitamin D3 in maintaining serum 25(OH)D levels (91), is effective in raising serum 25(OH)D concentrations above 50 nmol/L (20 ng/mL) only when the dose is increased to 800 IU/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 D3/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.

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...
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.

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 at least 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


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