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Vitamin D Deficiency: A Global Problem with Health Implications

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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_3/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.**

Keywords: **Vitamin D deficiency, common cancers, autoimmune diseases, physiologic concentrations.**

1. INTRODUCTION

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). 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 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

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D2 per 8 ounces was effective in eradicating rickets in the United States and Europe. The unfortunate outbreak of hypercalcemia in the 1950s in Great Britain was blamed on the overfortification of milk with vitamin D, even though there was little evidence for this (7). This was thought to extend the shelf-life of the vitamin D–fortified milk.

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 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 D_3. 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_2/mL (4, 10). In Canada, Europe, Japan, and India, vitamin D_3 is available as a pharmaceutical.

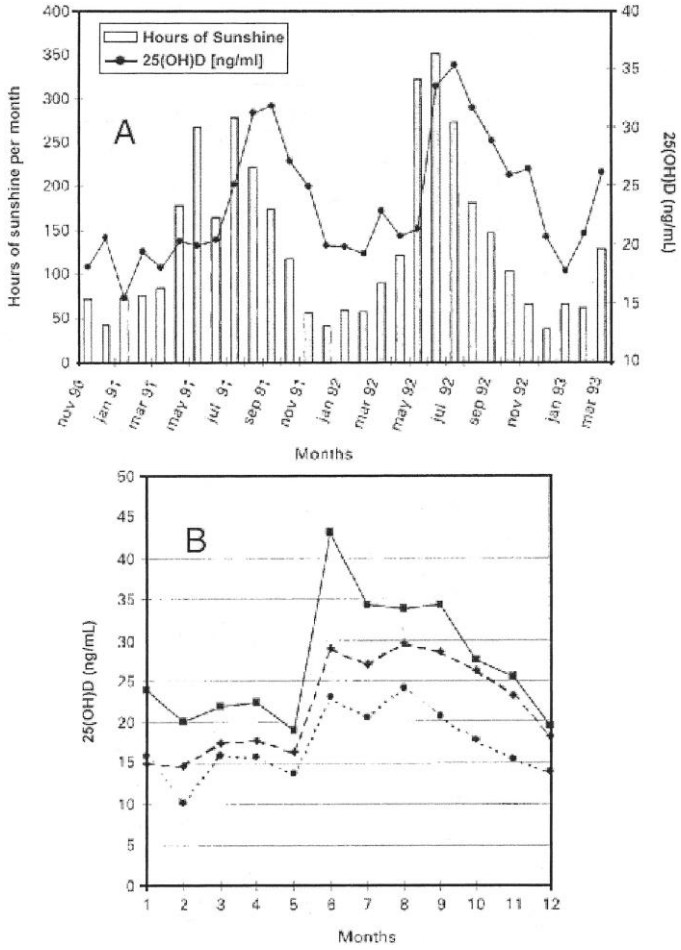

FIGURE 1. A: Relation between hours of sunshine and serum 25- hydroxyvitamin D [25(OH)D] concentrations. ■, hours of sunshine; F, 25(OH)D. B: Seasonal fluctuation in serum 25(OH)D according to frequency of sun exposure. ■, regular sun exposure; ♦, occasional sun exposure; F, avoiding direct sun exposure.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

CONSEQUENCES OF VITAMIN D DEFICIENCY ON THE MUSCULOSKELETAL SYSTEM

Most agree that a 25(OH)D concentration <50>30 ng/mL are considered to be sufficient (10 –15; Figure 2) This is based on the observation that intestinal calcium absorp- tion 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–

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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. 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. 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).

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 inter- feres with the penetration of UVB radiation into the skin will affect the cutaneous synthesis of vitamin D_3 (2, 9; **Figure 3**)

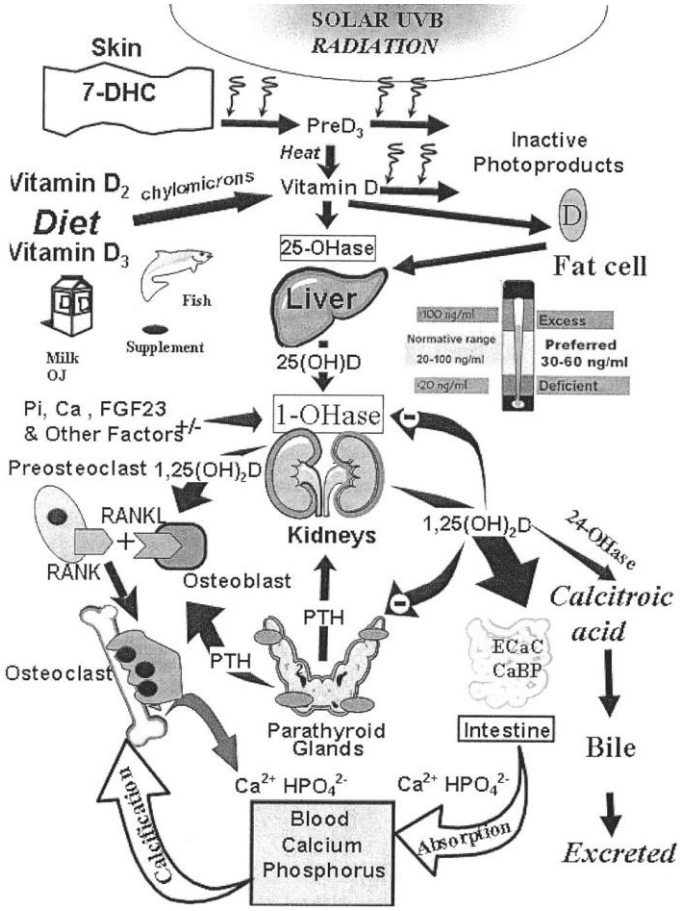

FIGURE 2. Schematic representation of the synthesis and metabolism of vitamin D for regulating calcium, phosphorus, and bone metabolism. During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D_3 ($preD_3$) and then by a heat-dependent process to vitamin D_3. Vitamin D (D represents D_2 or D_3) 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-1α-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 ca- tabolize $1,25(OH)_2D$ 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 NFnB ligand (RANKL). CaBP, calcium binding protein; ECaC, epithelial channel cal- cium; FGF23, fibroblast growth factor 23; OJ, orange juice; Pi, inorganic phosphate; PTH, parathyroid hormone; UVB, ultraviolet B radiation.

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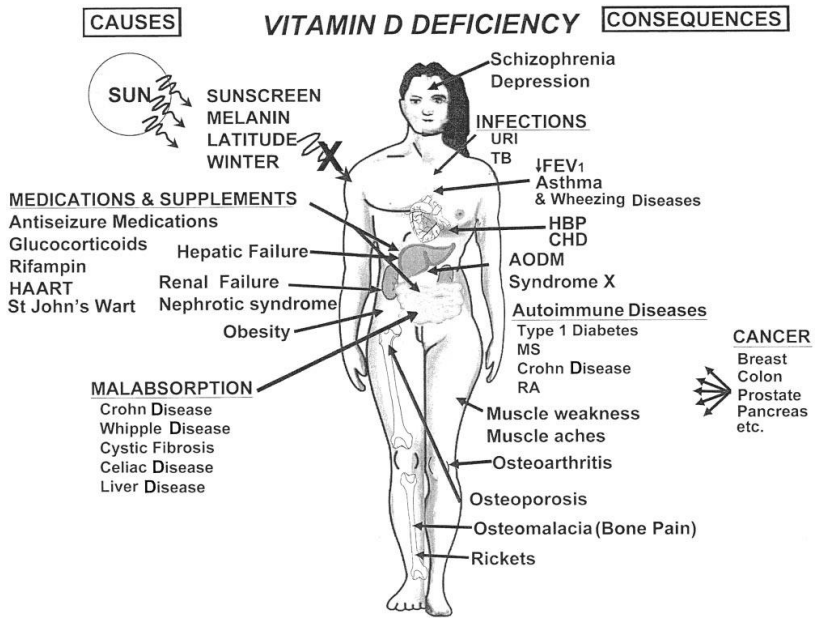

FIGURE 3. A schematic representation of the major causes of vitamin D deficiency and potential health consequences. AODM, adult onset diabetes mellitus; CHD, coronary heart disease; FEV_1, forced expiratory volume in 1 s; HAART, highly active antiretroviral therapy; HBP, high blood pressure; MS, multiple sclerosis; RA, rheumatoid arthritis; TB, tuberculosis; URI, urinary tract infection.

1. Melanin is extremely efficient in absorbing UVB radiation, and, 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). 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). 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).

PREVENTION AND TREATMENT OF VITAMIN DDEFICIENCY

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 govern- mental 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). 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). 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 capable of converting vitamin D to 25(OH)D (92).

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

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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 vita- min D2 may be equally effective as vitamin D3 in maintaining serum 25(OH)D concentrations.

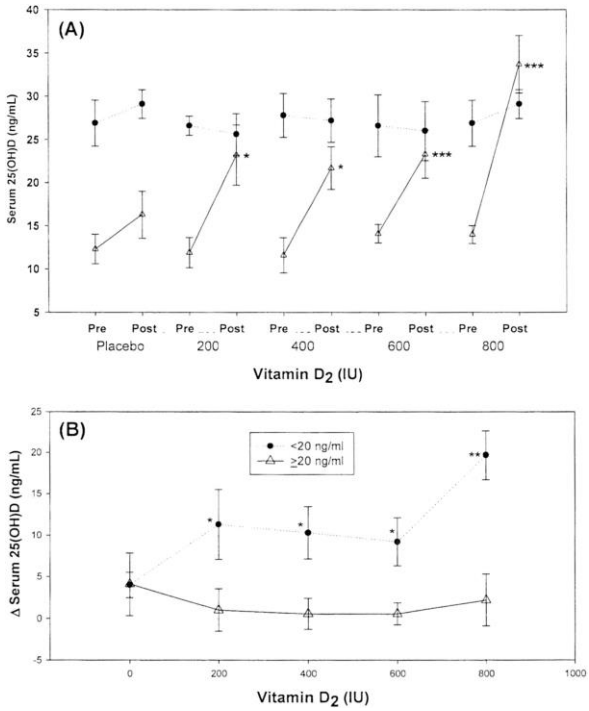

FIGURE 5. Mean (±SE) circulating concentrations (A) and changes (B) in 25-hydroxyvitamin D [25(OH)D]

2. CONCLUSION

Throughout evolution, humans have depended on the sun for their vitamin D requirement (1, 2). 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). 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. Neither of the authors had a conflict of interest.

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