The Vitamin D Epidemic and its Health Consequences[1–4]

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ABSTRACT   Vitamin D deficiency is now recognized as an epidemic in the United States. The major source of vitamin D for both children and adults is from sensible sun exposure. In the absence of sun exposure 1000 IU of cholecalciferol is required daily for both children and adults. Vitamin D deficiency causes poor mineralization of the collagen matrix in young children's bones leading to growth retardation and bone deformities known as rickets. In adults, vitamin D deficiency induces secondary hyperparathyroidism, which causes a loss of matrix and minerals, thus increasing the risk of osteoporosis and fractures. In addition, the poor mineralization of newly laid down bone matrix in adult bone results in the painful bone disease of osteomalacia. Vitamin D deficiency causes muscle weakness, increasing the risk of falling and fractures. Vitamin D deficiency also has other serious consequences on overall health and well-being. There is mounting scientific evidence that implicates vitamin D deficiency with an increased risk of type I diabetes, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and many common deadly cancers. Vigilance of one's vitamin D status by the yearly measurement of 25-hydroxyvitamin D should be part of an annual physical examination.   J. Nutr. 135: 2739S–2748S, 2005.

KEY WORDS: • vitamin D • osteoporosis • sunlight • 25-hydroxyvitamin D • cancer

Vitamin D, known as the "sunshine vitamin," has been taken for granted and, until recently, little attention has been focused on its important role for adult bone health and for the prevention of many chronic diseases. It has been assumed that vitamin D deficiency is no longer a health issue in the United States and Europe. However, it is now recognized that everyone is at risk for vitamin D deficiency.

Origin of vitamin D

Although it is not known when vitamin D was first made on Earth, it has been demonstrated that a phytoplankton species *Emiliani huxleii*, which has existed unchanged in the Atlantic Ocean for more than 750 million years, has the ability, when exposed to sunlight, to make vitamin D (1,2). As life forms evolved in the oceans, they took advantage of its high calcium content and used it as a mediator for a variety of metabolic functions, as well as for controlling neuromuscular activity. As vertebrates evolved, they found the ocean environment to be plentiful in calcium and therefore could take out of their environment the calcium required for a healthy mineralized skeleton (2). However, when vertebrates ventured onto the land masses, they needed to make vitamin D to enhance the efficiency of calcium absorption (1–3).

Sun-mediated production and regulation of cholecalciferol synthesis

During exposure to sunlight, ultraviolet B (UVB)[6] photons (290–315 nm) penetrate into the viable epidermis and dermis where they are absorbed by 7-dehydrocholesterol that is present in the plasma membrane of these cells (2). The absorption of UVB radiation causes 7-dehydrocholesterol to open its B ring, forming precholecalciferol (**Fig. 1**). Precholecalciferol is inherently unstable and rapidly undergoes rearrangement of its double bonds to form cholecalciferol. As cholecalciferol is being formed, it is ejected out of the plasma membrane into the extracellular space, where it enters into

[6] Abbreviations used: AI, adequate intake; DBP, vitamin D binding protein; IGF, insulin-like growth factor; MED, minimal erythemal dose; PTH, parathyroid hormone; SPF, sun protection factor; RANKL, receptor activator of NFκβ ligand; UVB, ultraviolet B; VDR, vitamin D receptor; VDRE, vitamin D responsive elements.
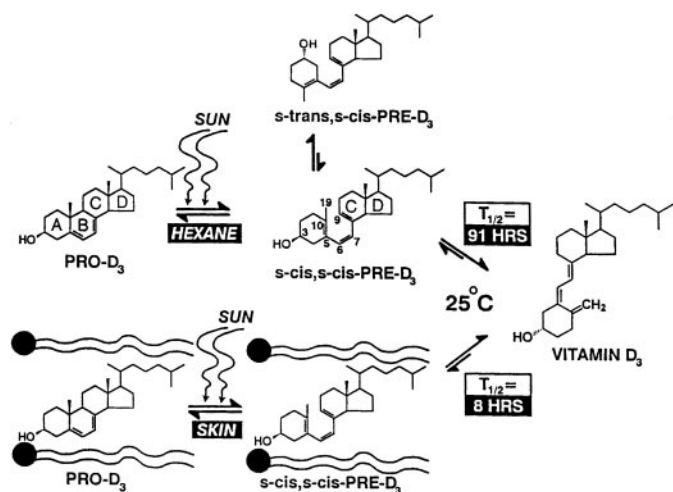
FIGURE 1 Photolysis of 7-dehydrocholesterol [procholecalciferol (pro-D-3)] into precholecalciferol (pre-D-3) and its thermal isomerization of cholecalciferol in hexane and in lizard skin. In hexane pro-D-3 is photolyzed to s-cis,s-*cis*-pre-D-3. Once formed, this energetically unstable conformation undergoes a conformational change to the s-trans,s-*cis*-pre-D-3. Only the s-cis,s-*cis*-pre-D-3 can undergo thermal isomerization to cholecalciferol. The s-cis,s-cis conformer of pre-D-3 is stabilized in the phospholipid bilayer by hydrophilic interactions between the 3β-hydroxyl group and the polar head of the lipids, as well as by the van der Waals interactions between the steroid ring and side-chain structure and the hydrophobic tail of the lipids. These interactions significantly decrease the conversion of the s-cis,s-cis conformer to the s-trans,s-cis conformer, thereby facilitating the thermal isomerization of s-cis,s-*cis*-pre-D-3 to cholecalciferol. Reproduced with permission (107).

the dermal capillary bed, drawn in by the vitamin D binding protein (DBP).

It was suggested that skin pigmentation evolved to prevent excess production of vitamin D in the skin (4). However, there has never been a reported case of vitamin D intoxication due to excessive exposure to sunlight for white lifeguards and sun worshippers or for tanners who frequent a tanning salon. The reason for this is that when precholecalciferol and cholecalciferol are exposed to sunlight, they undergo transformation of their double bonds to form a wide variety of photoisomers that have little biologic activity on calcium metabolism (2,5) (**Fig. 2**).

Melanin is an effective sunscreen and decreases vitamin D production in the skin (6). Above 37° latitude, during the fall and winter months, the zenith angle of the sun is very oblique, and therefore the solar UVB photons are efficiently absorbed resulting in little if any cholecalciferol made in the skin (2,7,8) (**Fig. 3**).

## Vitamin D metabolism and mechanisms of action

There are 2 major forms of vitamin D. Cholecalciferol (vitamin D-3) is produced in the skin after sun exposure. It is produced commercially by extracting 7-dehydrocholesterol from wool fat, followed by UVB irradiation and purification. Ergocalciferol (vitamin D-2) has a different side chain than cholecalciferol (i.e., a C_{24} methyl group and a double bond between C_{22} and C_{23}) and is commercially made by irradiating and then purifying the ergosterol extracted from yeast. Both vitamin D-2 and cholecalciferol are used to fortify milk, bread, and multivitamins in the United States. In Europe cholecal-

ciferol is almost exclusively used for multivitamins and food fortification.

Once vitamin D (either D-2 or D-3) is made in the skin or ingested in the diet, it undergoes 2 obligate hydroxylations, the first in the liver to 25-hydroxyvitamin D [25(OH)D] (9,10) (Fig. 2). 25(OH)D enters the circulation bound to its DBP and travels to the kidney where megalin translocates the DBP-25(OH)D complex into the renal tubule where in the mitochondria the 25-hydroxyvitamin D-1 α-hydroxylase ($CYP_{27}B$) introduces a hydroxyl function on C-1 to form 1α,25-dihydroxyvitamin D [1,25(OH)$_2$D] (9–11) (Fig. 2).

1,25(OH)$_2$D interacts with its nuclear vitamin D receptor
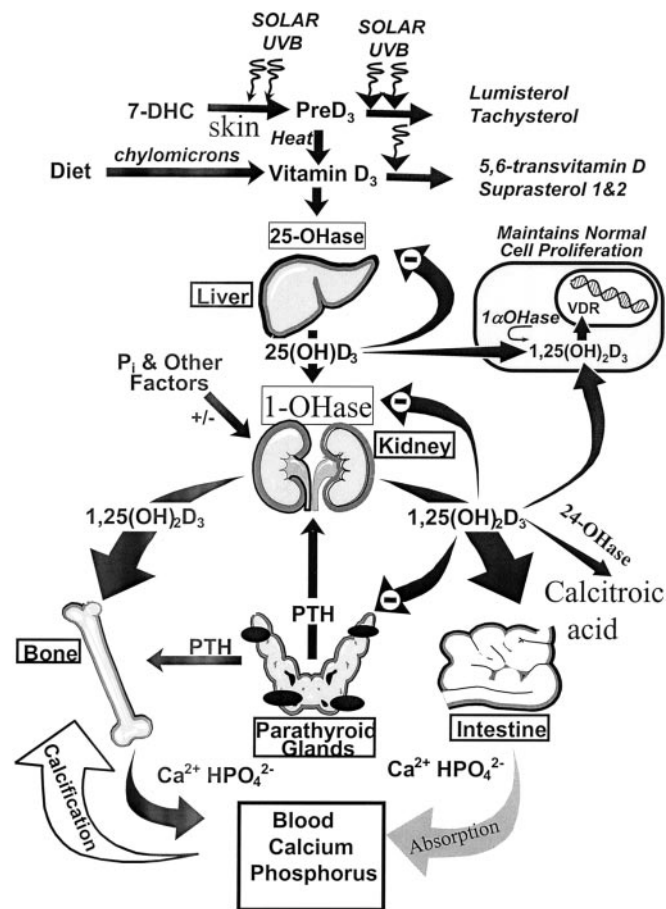
FIGURE 2 Schematic representation for cutaneous production of vitamin D and its metabolism and regulation for calcium homeostasis and cellular growth. During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin absorbs solar UVB radiation and is converted to precholecalciferol (pre-D-3). Once formed, D-3 undergoes thermally induced transformation to cholecalciferol. Further exposure to sunlight converts precholecalciferol and cholecalciferol to biologically inert photoproducts. Vitamin D coming from the diet or from the skin enters the circulation and is metabolized in the liver by the vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D-3 [25(OH)D-3]. 25(OH)D-3 re-enters the circulation and is converted in the kidney by the 25-hydroxyvitamin D-3–1α-hydroxylase (1-OHase) to 1,25-dihydroxyvitamin D-3 [1,25(OH)$_2$D-3]. A variety of factors, including serum phosphorus (P_i) and parathyroid hormone (PTH) regulated the renal production of 1,25(OH)$_2$D. 1,25(OH)$_2$D regulates calcium metabolism through its interaction with its major target tissues, the bone and the intestine. 1,25(OH)$_2$D-3 also induces its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase). 25(OH)D is metabolized in other tissues for the purpose of regulation of cellular growth. (Copyright Michael F. Holick, 2003, used with permission.)
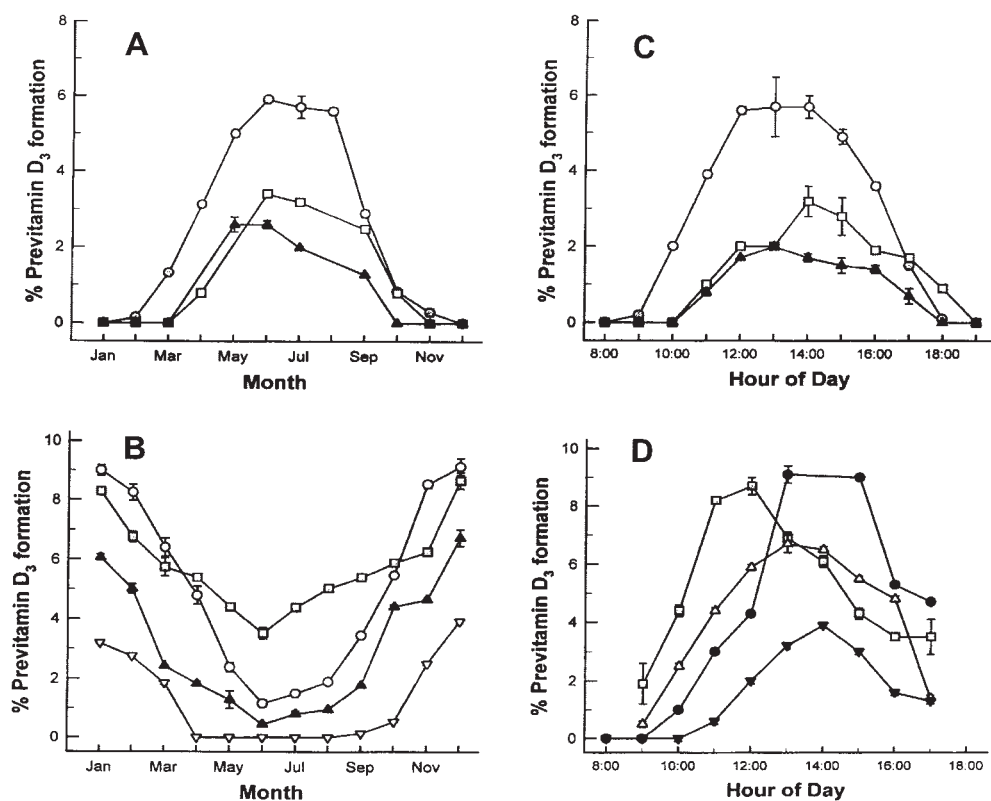
FIGURE 3 Influence of season, time of day in July, and latitude on the synthesis of precholecalciferol in northern (*A* and *C:* Boston -○-, Edmonton -□-, Bergen -▲-) and southern hemispheres (*B:* Buenos Aires -○-, Johannesburg -□-, Cape Town -▲-, Ushuala –▽- and *D:* Buenos Aires -●-, Johannesburg -□-, Cape Town -△-, Ushuala -▼-). The hour indicated in C and D is the end of the 1-h exposure time in July. Adapted from and reproduced with permission (Lu Z, Chen T, Kline L et al. Photosynthesis of precholecalciferol in cities around the world. In: M. Holick and A. Kligman, editors. Biologic effects of light. Proceedings. Berlin: Walter De Gruyter; 1992. p. 48–51).

(VDR), which in turn bonds with the retinoic acid-X-receptor. This complex is recognized by specific gene sequences known as the vitamin D responsive elements (VDRE) to unlock genetic information that is responsible for its biologic actions.

In the intestine $1,25(OH)_2D$ induces the expression of an epithelial calcium channel, calcium-binding protein (calbindin), and a variety of other proteins to help the transport of calcium from the diet into the circulation (11,12). $1,25(OH)_2D$ also interacts with its VDR in the osteoblast and stimulates the expression of receptor activator of $NF\kappa\beta$ ligand (RANKL) similar to parathyroid hormone (PTH) (10,13). Thus $1,25(OH)_2D$ maintains calcium homeostasis by increasing the efficiency of intestinal calcium absorption and mobilizing calcium stores from the skeleton.

PTH, hypocalcemia, and hypophosphatemia are the major stimulators for the renal production of $1,25(OH)_2D$ (10,11,14). During pregnancy, lactation, and the growth spurt, sex steroids, prolactin, growth hormone, and insulin-like growth factor 1 (IGF-1) play a role in enhancing the renal production of $1,25(OH)_2D$ to satisfy increased calcium needs (10,11).

Besides the small intestine and the osteoblast, the VDR has been identified in almost every tissue and cell in the body, including brain, heart, skin, pancreas, breast, colon, and immune cells (10,11,15). $1,25(OH)_2D$ helps regulate cell growth and maturation, stimulates insulin secretion, inhibits renin production, and modulates the functions of activated T and B lymphocytes and macrophages (10,11,16,17).

Consequence of vitamin D deficiency for bone health

In the late 1600s, as people migrated into industrialized cities in northern Europe, their children became afflicted with a crippling bone disease commonly known as rickets (**Fig. 4**). Rickets not only caused growth retardation but, due to the poorly mineralized skeleton, the long bones in the legs became deformed. In addition, vitamin D deficiency caused disruption in chondrocyte maturation at the ephyseal plates, leading to widening of the ends of the long bones and costochondral junctions. The disease was devastating because the growth retardation and bony deformities were not only disabling, but also childbearing women often had difficulty with birthing because of a flat and deformed pelvis (10).

Sniadecki, in 1822, suggested that the reason that children living in the industrialized cities of northern Europe developed rickets was because they were not exposed to sunlight (18). However, by the turn of the twentieth century, >80% of children living in industrialized cities in North America and Europe suffered from this bone-deforming disease.

It had been common practice on the coastlines of the United Kingdom and the Scandinavian countries to encourage children to take a daily dose of cod liver oil to prevent the disease (1–3). In 1919 Huldschinsky reported that children with rickets who were exposed to ultraviolet radiation from a mercury arc lamp for 1 h twice a week for 8 wk had marked radiological improvement of the disease (19,20) (**Fig. 5**). In 1921 Hess and Unger (21) demonstrated that sunlight could cure rickets when they exposed rachitic children to sunlight on the roof of a New York City hospital and demonstrated radiologically that the rickets had resolved. This led Hess and Weinstock to investigate independently the use of ultraviolet irradiation of food as a way of imparting antirachitic activity (22). Steenbock (23) appreciated its utility and introduced the concept of irradiating milk as a means of preventing rickets in children. This led to the fortification of milk with vitamin D, which helped eradicate rickets in the United States and in countries that used this fortification practice.
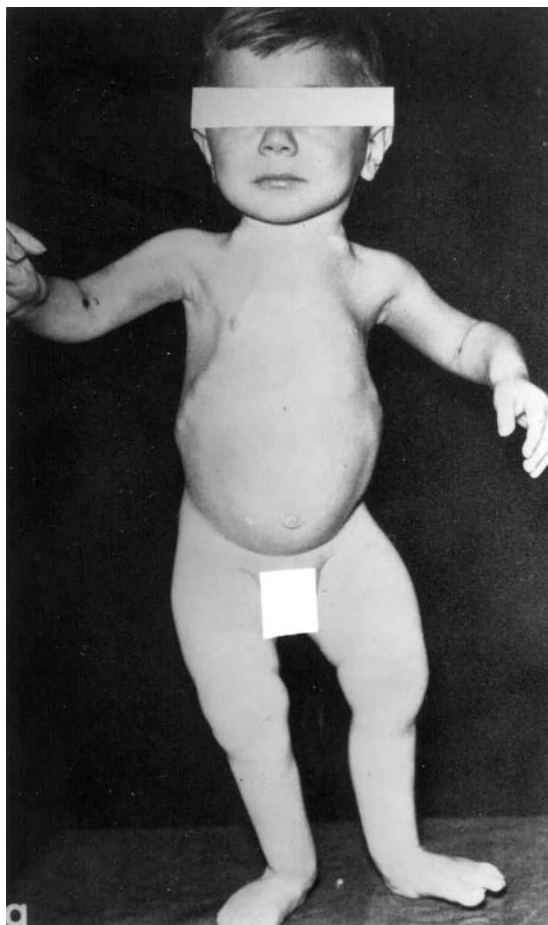
FIGURE 4 Child with rickets.

A deficiency in vitamin D results in a decrease in the efficiency of intestinal absorption of dietary calcium and phosphorus (10,11,24). This causes a transient lowering of the ionized calcium, which is immediately corrected by the increased production and secretion of PTH. PTH sustains the blood-ionized calcium by interacting with its membrane receptor on mature osteoblasts, which induces the expression of RANKL (10,13). This plasma membrane receptor protein is recognized by RANK, which is present on the plasma membrane of preosteoclasts. The intimate interaction between RANKL and RANK results in increased production and maturation of osteoclasts (10,11,13). PTH also decreases the gene expression of osteoprotegerin (a RANKL-like receptor that acts as a decoy) in osteoblasts, which further enhances osteoclastogenesis (25). The osteoclasts release hydrochloric acid and collagenases to destroy bone, resulting in the mobilization of the calcium stores out of the skeleton. Thus vitamin D deficiency induced secondary hyperparathyroidism results in the wasting of the skeleton, which can precipitate and exacerbate osteoporosis.

Vitamin D deficiency and attendant secondary hyperparathyroidism also causes a loss of phosphorus into the urine and a lowering of serum phosphorus levels. This results in an inadequate calcium $\times$ phosphorus product, causing poor or defective mineralization of the bone matrix laid down by osteoblasts (26,27). In children, the poorly mineralized skeleton under the weight of the body and the gravity results in the classic bony rachitic deformities in the lower limbs (bowed legs or knocked knees) (Fig. 4). Adults have enough mineral in their skeleton to prevent skeletal deformities. However, in a vitamin D deficient state, the newly laid-down osteoid cannot be properly mineralized, leading to osteomalacia. Unlike osteoporosis, which is a silent disease until fracture occurs, osteomalacia is associated with either global or isolated throbbing bone pain that is often misdiagnosed as fibromyalgia, myositis, or chronic fatigue syndrome (28–30). The likely cause is that the unmineralized osteoid becomes hydrated and provides little support for the sensory fibers in the periosteal covering (31). This is translated to the patient as throbbing, aching bone pain. This can be easily elicited by pressing the forefinger or the thumb on the sternum, the anterior tibia, or the midshaft of the radius or the ulna, and eliciting bone discomfort. It should be noted that you cannot distinguish osteoporosis/osteopenia from osteomalacia either by X-ray analysis or by bone densitometry; they look the same.

Factors that affect vitamin D status

Aging (32), increased skin pigmentation (33), and obesity (34) are associated with vitamin D deficiency. 7-dehydrocholesterol levels in the skin decline with age (35). A 70-y-old person has ~25% of the capacity to produce cholecalciferol compared with a healthy young adult (36). Sunscreens are effective at preventing sunburning and skin damage, because they efficiently absorb solar UVB radiation. When used properly, a sunscreen with a sun protection factor (SPF) of 8 reduces the capacity of the skin to produce cholecalciferol by 95% (37). Adults who always wear a sunscreen before going outside are at higher risk for vitamin D deficiency (38). Melanin is an extremely effective UVB sunscreen. Thus, African Americans who are heavily pigmented require at least 5 to 10 times longer exposure than whites to produce adequate cholecalciferol in their skin (6) (**Fig. 6**).

Vitamin D, being fat soluble, is stored in the body fat. Cholecalciferol that is produced in the skin or ingested from the diet is partially sequestered in the body fat. This store of cholecalciferol is used during the winter when the sun is incapable of producing cholecalciferol. However, in obese children and adults, the cholecalciferol is sequestered deep in the body fat, making it more difficult for it to be bioavailable. Thus, obese individuals are only able to increase their blood levels of vitamin D ~50% compared with normal weighted individuals (34) (**Fig. 7**).
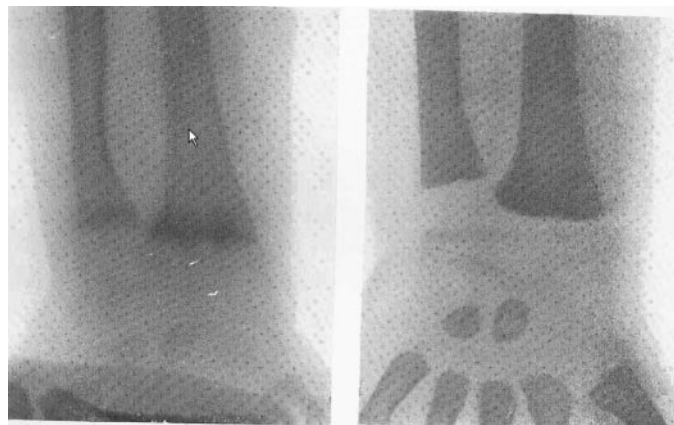
FIGURE 5 Florid rickets of severe degree. Radiograms taken before (*left panel*) and after treatment with 1 h UVR 2 times/wk for 8 wk. Note mineralization of the carpal bones and epiphyseal plates (*right panel*) [in the public domain, ref. (106)].
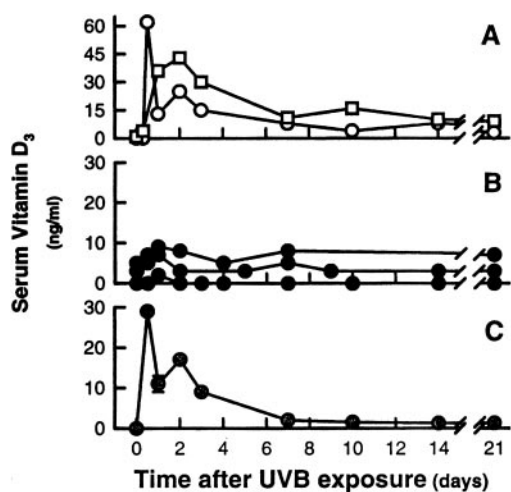
FIGURE 6 Change in serum concentrations of vitamin D-3 in 2 lightly pigmented white (skin type II) (*A*) and 3 heavily pigmented African American subjects (skin type V) (*B*) after total-body exposure to 54 mJ/cm² of UVB radiation. (*C*) Serial change in circulating concentrations of cholecalciferol after re-exposure of one black subject in *panel B* to a 320 mJ/cm² dose of UVB radiation. Reproduced with permission (6).

Recommended adequate intake and sources of vitamin D from diet, sunlight, and UV light sources

Very little vitamin D is naturally present in our food. Oily fish, including salmon, mackerel, and herring; cod liver oil; and sun-dried mushrooms typically provide 400–500 IU of vitamin D per serving. The major foods that are fortified with vitamin D in the United States include milk, orange juice, cereals, and some breads. Some yogurts and cheeses now are being fortified with vitamin D, whereas other dairy products are not (10,26). In Europe, most countries forbid the fortification of milk with vitamin D. These countries permit margarine and some cereals to be vitamin D fortified (39).

Our skin is the major source of vitamin D; 90–95% of most people's vitamin D requirement comes from casual sun exposure. An adult Caucasian exposed to sunlight or a (tanning bed) lamp (~32 mJ/cm²) that emits UVB radiation produces ~1 ng of cholecalciferol/cm² of skin. Exposure of the skin to one minimal erythemal dose (MED) (a slight pinkness to the skin), raises the blood level of cholecalciferol to a level comparable to a person taking ~10,000–20,000 IU of vitamin D-2 (26) (**Fig. 8**). Although aging decreases the amount of 7-dehydrocholesterol on the skin, elders exposed to sunlight are capable of making enough cholecalciferol to satisfy their needs (40).

There are a variety of multivitamin supplements that contain 400 IU of either vitamin D-2 or cholecalciferol. Vitamin D-2 and cholecalciferol supplements are also available in either 400 or 1000 IU capsules or tablets. The recommended adequate intake (AI) of vitamin D for children and adults up to 50 y is 200 IU, whereas the recommended AI for adults 51–70 y and 71+ y is 400 IU and 600 IU, respectively (40,41).

Determination of vitamin D status

The measurement of the major circulating form of vitamin D, 25(OH)D, is the gold standard for determining the vitamin D status of a patient. The normal range, which is typically 25–37.5 nmol/L (10–15 ng/mL) to 137.5–162.5 nmol/L (55–65 ng/mL) by most commercial assays, is not truly reflec-

tive of whether a patient is vitamin D deficient or intoxicated. Most studies suggest that the PTH levels plateau and are at their ideal physiologic concentration when the serum 25(OH)D is above 80 nmol/L (32 ng/mL) (42–44). Vitamin D intoxication that includes hypercalcemia, typically, is not observed until the 25(OH)D reach levels of at least 375 nmol/L (150 ng/mL) (45). The measurement of 1,25(OH)₂D provides no insight about the vitamin D status of a patient. It is often normal or on occasion elevated in vitamin D deficient patients. The reasons are that 1,25(OH)₂D levels are 1000 times lower than 25(OH)D levels and the secondary hyperparathyroidism increases the renal production of 1,25(OH)₂D (26).

Treatment for vitamin D deficiency

It has been estimated that the body uses daily on average 3,000–5,000 IU of cholecalciferol (46). Recent studies suggest that in the absence of sun exposure, 1000 IU of cholecalciferol is needed to maintain a healthy 25(OH)D of at least 78 nmol/L (30 ng/mL) (46,47) (**Fig. 9**). Vitamin D-2 is more rapidly catabolized than cholecalciferol, thus vitamin D-2 is
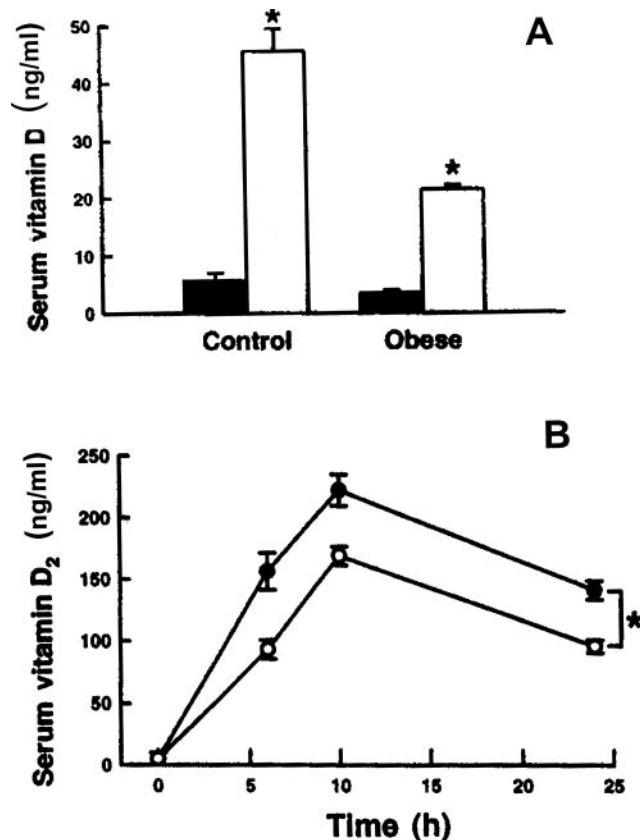
FIGURE 7 (*A*) Mean (±SEM) serum cholecalciferol, concentrations in obese (BMI > 30) and normal weighted adults before (■) and 24 h after (□) whole-body irradiation (27 mJ/cm²) with UVB radiation. The response of the obese subjects was attenuated when compared with that of the control group. There was a significant time-by-group interaction, $P = 0.003$. *Significantly different from before values ($P < 0.05$). (*B*) Mean (±SEM) serum vitamin D-2 concentrations in the control (●) and obese (○) groups before and after 25 h after oral intake of vitamin D-2 (50,000 IU, 1.25 mg). *Significant time and group effects by ANOVA ($P < 0.05$) but no significant time-by-group interaction. The difference in peak concentrations between obese and nonobese control subjects was not significant. Reproduced with permission (34).
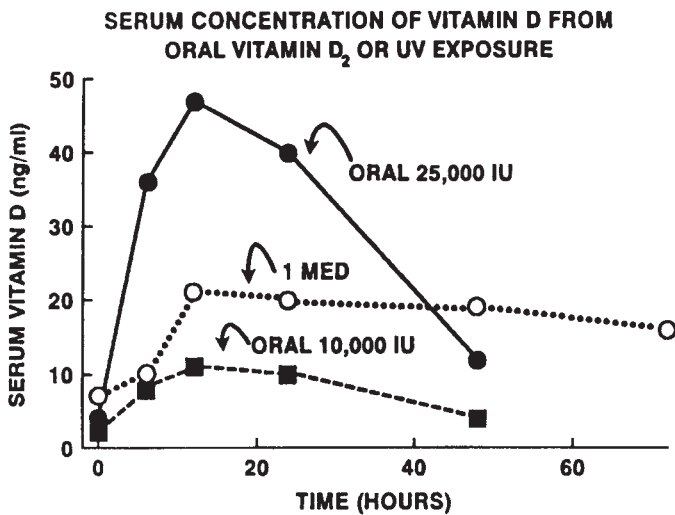
FIGURE 8 Serum vitamin D concentrations after a whole-body exposure to 1 MED (of simulated sunlight in a tanning bed and after a single oral dose of either 10,000 or 25,000 IU vitamin D-2. Reproduced with permission (26).

only about 20–40% as effective as cholecalciferol in maintaining serum concentrations of 25(OH)D (48,49).

Patients with intestinal fat malabsorption syndromes, such as Crohn's disease, Whipple's disease, cystic fibrosis, and Sprue, are often vitamin D deficient (10,11,26,50). This is because they are unable to efficiently absorb the fat-soluble vitamin into the chylomicrons, resulting in malabsorption (52). Because the metabolic pathways in the liver and the kidneys are not compromised, the best method to correct vitamin D deficiency in these patients is to encourage either sensible exposure to sunlight or a lighting system that emits UVB radiation, such as a tanning bed (52). Several commercial UVB lamps that are marketed as sun tanning lamps are also effective in producing cholecalciferol in the skin (53,54). A patient with Crohn's disease with only 2 feet of small intestine was able to raise her blood level of 25(OH)D 700% and to 100 nmol/L (40 ng/mL) after exposure to a tanning bed that emitted UVB radiation 3 times a week for 3 mo (55).

For most patients with vitamin D deficiency, filling the empty vitamin D tank as quickly as possible is the goal. The only pharmaceutical preparation of vitamin D in the United States is vitamin D-2. Although it is only 20–40% as effective as cholecalciferol in raising blood levels of 25(OH)D, it does work if given in high enough doses. Typically, patients receiving 50,000 IU of vitamin D-2 once a week for 8 wk will correct vitamin D deficiency (56) (**Fig. 10**). This can be followed by giving 50,000 U of vitamin D once every other week to maintain vitamin D sufficiency.

Role of vitamin D in cancer prevention

In 1941, Apperley (57) reported a curious observation, i.e., that people who lived in northern latitudes in the United States, including Massachusetts, Vermont, and New Hampshire, were more likely to die of cancer than adults living in Texas, South Carolina, and other southern states. He noted that although people living in southern states were more likely to develop nonlife-threatening skin cancer, he suggested that this provided an immunity for the more serious cancers of breast, colon, and prostate that were lethal. Little attention was paid to this startling observation until the late 1980s,

when Garland et al. (58) reported that colon cancer mortality was much higher in the northeastern United States compared with people living in southern states. It is now well documented that the risk of developing and dying of colon, prostate, breast, ovarian, esophageal, non-Hodgkin's lymphoma, and a variety of other lethal cancers is related to living at higher latitudes and being more at risk of vitamin D deficiency (58–62).

Initially the explanation for why increased sun exposure decreased the risk of dying of common cancers was due to the increased production of vitamin D in the skin, which led to the increased production of $1,25(OH)_2D$ in the kidneys (58). Because it was known that the VDR existed in most tissues in the body and that $1,25(OH)_2D$ was a potent inhibitor of both normal and cancer cell growth (2,10,63,64), it was assumed that the increased renal production of $1,25(OH)_2D$ could in some way downregulate cancer cell growth and therefore mitigate the cancer's activity and decrease mortality. However, it was also known that the production of $1,25(OH)_2D$ in the kidneys was tightly controlled and that increased intake of vitamin D or exposure to sunlight did not result in an increase in the renal production of $1,25(OH)_2D$ (10,11). Increased ingestion of vitamin D or increased production of cholecalciferol in the skin results in an increase in circulating concentrations of 25(OH)D. However, this still did not explain the anti-cancer effect of the sunlight-vitamin D connection.

The skin not only makes cholecalciferol, but it also has the enzymatic machinery to convert 25(OH)D to $1,25(OH)_2D$ similar to activated macrophages (65,66). In 1998 Schwartz et al. (67) reported normal and malignant prostate cancer cells also had the enzymatic machinery to make $1,25(OH)_2D$. This observation helped to crystallize the important role of vitamin D in cancer prevention. Increased exposure to sunlight or vitamin D intake leads to increased production of 25(OH)D.
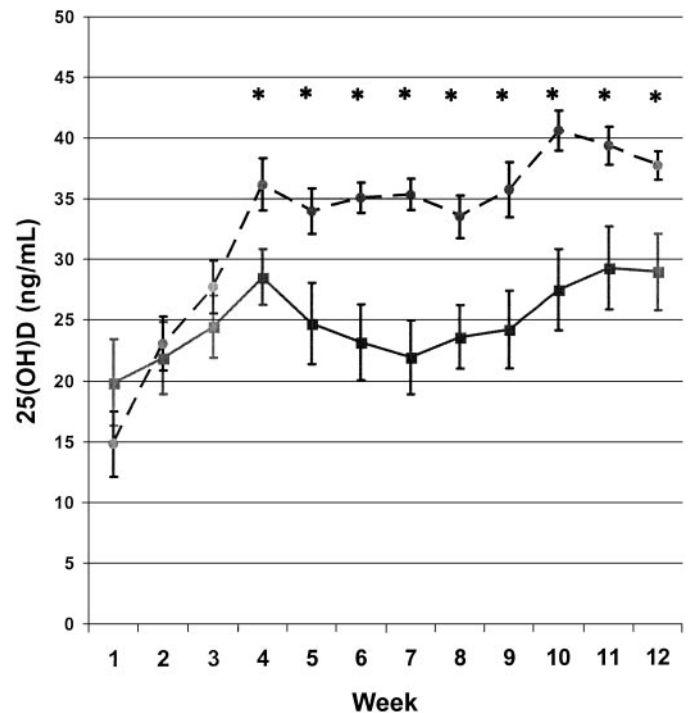
FIGURE 9 Mean (±SEM) weekly 25-hydroxyvitamin D [25(OH)D] concentration in healthy adults ingesting orange juice fortified with vitamin D (1000 IU, 8 oz^{-1} · d^{-1}, ●) or unfortified orange juice (■). *$P \leq 0.01$. Reproduced with permission (47).
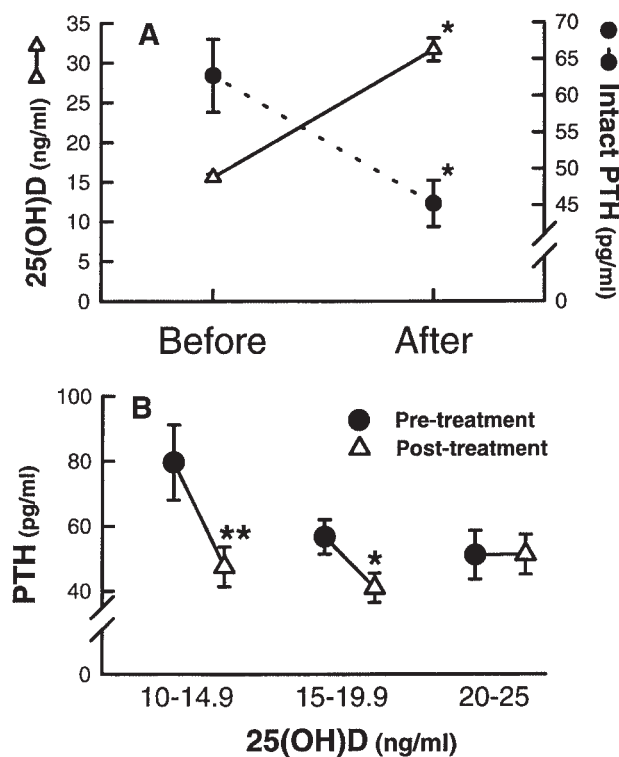
FIGURE 10 (A) Serum levels of 25(OH)D (-Δ-) and PTH (-o-) before and after therapy with 50,000 IU of vitamin D-2 and calcium supplementation once a week for 8 wk. (B) Serum levels of PTH levels in patients who had serum 25(OH)D levels of between 25 and 75 nmol/L (10 and 25 ng/mL) and who were stratified in increments of 12.5 nmol/L (5 ng/mL) before and after receiving 50,000 IU of vitamin D-2 and calcium supplementation for 8 wk. Reproduced with permission (56).

Higher concentrations of 25(OH)D are used by the prostate cells to make 1,25(OH)$_2$D, which helps keep prostate cell proliferation in check and therefore decreases the risk of prostate cells becoming malignant (10,63,64) (**Fig. 11**).

Since this observation, it has been observed that breast, colon, lung, brain, and a wide variety of other cells in the body have the enzymatic machinery to make 1,25(OH)$_2$D (10,26,68–72). Thus it has been suggested that raising blood levels of 25(OH)D provides most of the tissues in the body with enough substrate to make 1,25(OH)$_2$D locally to serve as a sentinel to help control cellular growth and maturation and to decrease the risk of malignancy (10).

This hypothesis has been further supported by the observation that both prospective and retrospective studies revealed that, if the 25(OH)D level is at least 20 ng/mL, then there is a ~30–50% decreased risk of developing and dying of colon, prostate, and breast cancers (10,58,59,62,64).

Vitamin D and autoimmune disease prevention

Activated T and B lymphocytes, monocytes, and macrophages have a VDR (16,72–74). 1,25(OH)$_2$D interacts with its VDR in immune cells and has a variety of effects on regulating lymphocyte function, cytokine production, macrophage activity, and monocyte maturation (10,16,17,72–74). Thus, 1,25(OH)$_2$D is a potent immunomodulator.

Insights into the important role of vitamin D in the prevention of autoimmune diseases have come from a variety of animal studies. Nonobese diabetic mice that typically develop type 1 diabetes by 200 d of age reduced their risk of developing

this disease by 80% when they received a physiologic dose of 1,25(OH)$_2$D-3 daily (75). Mice that were pretreated with 1,25(OH)$_2$D-3 before they were injected with myelin to induce a multiple-sclerosis-like disease were immune from it (76). Similar observations were made in a mouse model that develops Crohn's disease (77).

These animal model studies have given important insights into the role of 1,25(OH)$_2$D in reducing the risk of developing common autoimmune diseases. It is now recognized that living at a latitude above 37° increases risk of developing multiple sclerosis throughout life by >100% (78). Furthermore, taking a multivitamin that contains 400 IU of vitamin D reduces risk of developing multiple sclerosis by ~40% (79). Women taking 400 IU of vitamin D in a multivitamin decreased their risk of rheumatoid arthritis by ~40% (80). Most compelling is the observation that children in Finland who received 2000 IU of vitamin D a day from 1 y of age on and who were followed for the next 25 y had an 80% decreased risk of developing type 1 diabetes, whereas children who were vitamin D deficient had a 4-fold increased risk of developing this disease later in life (81).

Vitamin D and the prevention of hypertension and cardiovascular heart disease

In 1979 Rostand (82) reported that people living at higher latitudes throughout the world were at higher risk of having hypertension. He had suggested that this may in some way be related to their being more prone to developing vitamin D deficiency. To determine the possible link between sun exposure and the protective effect in preventing hypertension, Krause et al. (83) exposed a group of hypertensive adults to a tanning bed that emitted light and UVB and UVA radiation similar to summer sunlight. A similar group of hypertensive adults was exposed to a similar tanning bed that emitted light and UVA radiation similar to winter sunlight, i.e., no UVB radiation. All subjects were exposed 3 times a week for 3 mo. After 3 mo, it was observed that hypertensive patients who were exposed to the tanning bed that emitted UVB radiation had a 180% increase in their circulating concentrations of
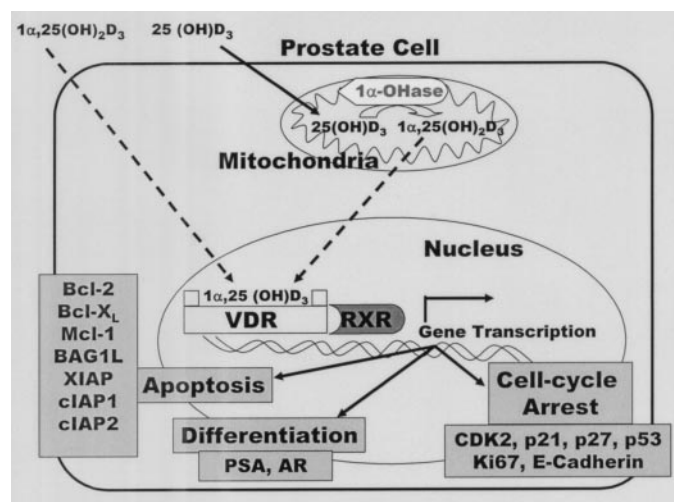
FIGURE 11 1,25(OH)$_2$D-3 regulates prostate cell growth by interacting with its nuclear VDR to alter the expression of genes that regulate cell-cycle arrest, apoptosis, and differentiation. 25(OH)D is metabolized in the prostate cell to 1,25(OH)$_2$D, which regulates cell growth.

25(OH)D. There was no change in the blood levels of 25(OH)D in the comparable patients who were exposed to the tanning bed that did not emit UVB radiation. The patients who had increased 25(OH)D levels also had a decrease of 6 mm Hg in their systolic and diastolic blood pressures, bringing them into the normal range, whereas the group that was exposed to the tanning bed that did not emit UVB radiation and did not change their 25(OH)D levels had no effect on their blood pressure.

It has also been observed that patients with cardiovascular heart disease are more likely to develop heart failure if they are vitamin D deficient (84). Furthermore, patients with peripheral vascular disease and the common complaint of lower leg discomfort (claudication) were often found to be vitamin D deficient. The muscle weakness and pain was not due to the peripheral vascular disease but because of the vitamin D deficiency (85).

Although the exact mechanism involved in how vitamin D sufficiency protects against cardiovascular heart disease is not fully understood, it is known that $1,25(OH)_2D$ is one of the most potent hormones for downregulating the blood pressure hormone renin in the kidneys (86). Furthermore, there is an inflammatory component to atherosclerosis, and vascular smooth muscle cells have a VDR and relax in the presence of $1,25(OH)_2D$ (87,88). Thus, there may be a multitude of mechanisms by which vitamin D is cardioprotective. The observation by Teng et al. (89) that renal failure patients who received the $1\alpha,25(OH)_2D$-3 analog, paracalcitol, were less likely to die of cardiovascular complications helps to support the importance of vitamin D for cardiac health.

Conclusions

It had been estimated that the body requires daily 3000–5000 IU of vitamin D (46). The most likely reason for this is that essentially every tissue and cell in the body has a VDR and therefore has a requirement for vitamin D. Vitamin D is critically important for the maintenance of calcium metabolism and good skeletal health throughout life. It is now recognized that maintenance of a serum 25(OH)D level of 80 nmol/L (32 ng/mL) or greater improves muscle strength (90,91) and bone mineral density in adults (52,92). The recent revelations that vitamin D regulates the immune system, controls cancer cell growth and regulates the blood pressure hormone renin provides an explanation for why vitamin D sufficiency has been observed to be so beneficial in the prevention of many chronic illnesses that plague both children and adults (Fig. 12).

Vitamin D deficiency is an unrecognized epidemic in both children and adults throughout the world (93–98), even in some of the sunniest climates, including Saudi Arabia and India (99,100). A recent survey of the vitamin D intake in the United States revealed that neither children nor adults are receiving the recommended AIs for vitamin D (101). The public health consequences of vitamin D deficiency are incalculable. This is especially true for people more prone to vitamin D deficiency, including people of darker skin color. It is well documented that African Americans are more prone to developing colon, prostate, breast, and a wide variety of other cancers, and that these cancers are much more aggressive compared with the white population. In addition, they are more likely to develop type 1 diabetes and hypertension, and are at high risk for vitamin D deficiency (102,103). Thus, vitamin D status has such important health implications that a measurement of 25(OH)D should be part of a routine physical examination for children and adults of all ages.
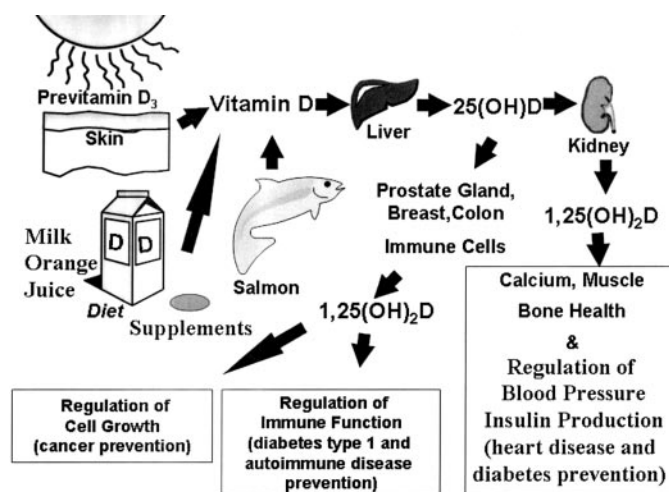
FIGURE 12 Schematic representation of the multitude of other potential physiologic actions of vitamin D for cardiovascular health, cancer prevention, regulation of immune function and decreased risk of autoimmune diseases. (Copyright Michael F. Holick, 2003, used with permission.)

Sensible sun exposure in the spring, the summer, and the fall (not during the winter unless one is located below 35° north), and education of the public about the beneficial effects of some limited sun exposure to satisfy their body's vitamin D requirements should be implemented. It is well documented that excessive exposure to sunlight and sunburning experiences while as a child or young adult increases the risk of nonmelanoma skin cancer that is often easily curable (104). There are several studies that suggest that increased exposure to limited amounts of sunlight decreases risk of developing and dying of the most deadly form of skin cancer, melanoma (104,105).

In the absence of any sun exposure, 1000 IU of cholecalciferol a day is necessary to maintain a healthy blood level of 25(OH)D of between 80 and 100 nmol/L. Dietary sources and vitamin D supplements can satisfy this requirement. Increasing intake of vitamin D fortified foods such as milk and orange juice, and increasing fatty fish consumption will help satisfy the body's requirement for vitamin D in the absence of exposure to sunlight. Multivitamins typically contain 400 IU of vitamin D, and there are several manufacturers that provide a vitamin D-2 or cholecalciferol supplement as either 400 or 1000 IU. Thus, diet plus additional vitamin D supplementation can result in attaining the recommended 1000 IU of cholecalciferol.

It has been estimated that exposure to sunlight for usually no more than 5–15 min/d (between 10 AM and 3 PM) on arms and legs or hands, face and arms, during the spring, the summer, and the fall, provides the body with its required 1000 IU of cholecalciferol. After the limited exposure, this should be followed by the application of a broad spectrum sunscreen with an SPF of at least 15 to prevent damaging effects due to excessive exposure to sunlight and to prevent sun burning. Thus, increasing vitamin D intake from vitamin D fortified foods, and vitamin D supplements, in combination with sensible sun exposure, should maximize a person's vitamin D status to promote good health (8).

LITERATURE CITED

1. Holick MF. Phylogenetic and evolutionary aspects of vitamin D from phytoplankton to humans. In: Pang PKT, Schreibman MP, editors. Vertebrate

endocrinology: fundamentals and biomedical implications. Vol. 3. Orlando: Academic Press; 1989. p. 7–43.

2. Holick MF. Vitamin D. A millennium perspective. J Cell Biochem. 2003; 88:296–307.

3. Holick MF. Evolution, biologic functions, and recommended dietary allowances for vitamin D. In: M.F. Holick, editor. Vitamin D: physiology, molecular biology and clinical applications. Totowa, NJ: Humana Press; 1998. p. 1–16.

4. Loomis WF. Although it is still widely regarded as a dietary-deficiency disease resulting from a lack of "vitamin D," it results in fact from a lack of sunlight. In smoky cities it was the first air-pollution disease. Sci Am. 1970;8:77.

5. Holick MF, MacLaughlin JA, Dobbelt SH. Regulation of cutaneous previtamin D_3 photosynthesis in man: skin pigment is not an essential regulator. Science. 1981;211:590–3.

6. Clemens TL, Henderson SL, Adams JS, Holick MF. Increased skin pigment reduces the capacity of skin to synthesize vitamin D_3. Lancet. 1982;1: 74–6.

7. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D_3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. J Clin Endocrinol Metab. 1988;67:373–8.

8. Holick MF. The UV Advantage. New York: ibooks; 2004.

9. Darwish H, DeLuca HF. Vitamin D-regulated gene expression. Crit Rev Eukaryot Gene Expr. 1993;3:89–116.

10. Holick MF. Vitamin D. Importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 2004;79:362–71.

11. Bouillon R. Vitamin D: from photosynthesis, metabolism, and action to clinical applications. In: DeGroot LJ, Jameson JL, editors. Endocrinology. Philadelphia: W.B. Saunders; 2001. p. 1009–28.

12. Christakos S, Liu Y, Dhawan P, Peng X. The calbindins: calbindin-D_{9K} and calbindin-D_{28K}. In: Feldman D, Pike JW, Glorieux FH, editors. Vitamin D. 2nd ed. London: Elsevier; 2005. p. 721–35.

13. Khosla S. The OPG/RANKL/RANK system. Endocrinology. 2001;142: 5050–5.

14. Portale AA, Booth BE, Halloran BP, Morris RC Jr. Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. J Clin Invest. 1984;73:1580–9.

15. Stumpf WE, Sar M, Reid FA, Tanaka Y, DeLuca HF. Target cells for 1,25-dihydroxyvitamin D_3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid. Science. 1979;206:1188–1190.

16. Adorini L. 1,25-Dihydroxyvitamin D_3 analogs as potential therapies in transplantation. Curr Opin Investigat Drugs. 2002;3:1458–63.

17. DeLuca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J. 2001;15:2579–85.

18. Sniadecki J, Jerdrzej Sniadecki (1768–1838) on the cure of rickets. (1840) Cited by W. Mozolowski. Nature. 1939;143:121–4.

19. Huldschinsky K. Heilung von Rachitis durch Kunstliche Hohensonne Deutsche Med Wochenschr. 1919;45:712–3.

20. Huldschinsky K. The ultra-violet light treatment of rickets NJ: Alpine Press; 1928. pp. 3–19.

21. Hess AF, Unger LJ. The cure of infantile rickets by sunlight. J. Am. Med. Ass. 1921;77:39–41.

22. Hess AF, Weinstock M. Antirachitic properties imparted to inert fluids and to green vegetables by ultraviolet irradiation. J Biol Chem. 1924;62:301–13.

23. Steenbock H. The induction of growth-prompting and calcifying properties in a ration exposed to light. Science. 1924;60:224–5.

24. Holick MF. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus M, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 5th ed. Washington, DC: American Society for Bone and Mineral Research; 2003. p. 129–37.

25. Huang JC, Sakata T, Pfleger LL, Bencsik M, Halloran P, Bikle DD, Nissenson RA. PTh differentially regulates expression of RANKL and OPG. J Bone Miner Res. 2004;19:235–44.

26. Holick MF. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health Curr Opin Endocrinol Diabetes. 2002;9: 87–98.

27. Stamp TC, Walker PG, Perry W, Jenkins MV. Nutritional osteomalacia and late rickets in greater London, 1974–1979: clinical and metabolic studies in 45 patients. Clin Endocrinol Metab. 1980;9:81–105.

28. Holick MF. Vitamin D deficiency: what a pain it is. Mayo Clin Proc. 2003;78:1457–9.

29. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc. 2003; 78:1463–70.

30. Glerup H, Middelsen K, Poulsen L, Hass E, Overbeck S, Andersen H, Charles P, Eriksen EF. Hypovitaminosis D myopathy without biochemical signs of ostemalacia bone involvement. Calcif Tissue Int. 2000;66:419–24.

31. Holick MF. Sunlight and vitamin D: both good for cardiovascular health. J Gen Intern Med. 2002;17:733–5.

32. Salamone LM, Dalla GE, Zantos D, Makrauer F, Dawson-Hughes B. Contributions of vitamin D intake and seasonal sunlight exposure to plasma 25-hydroxyvitamin D concentration in elderly women. Am J Clin Nutr. 1993;58: 80–6.

33. Kyriakidou-Himonas M, Aloia JF, Yeh JK. Vitamin D supplementation in postmenopausal black women. J Clin Endocrinol Metab. 1999;84:3988–90.

34. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72:690–3.

35. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D_3. J Clin Invest. 1985;76:1536–8.

36. Holick MF, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. Lancet. 1989;II:1104–5.

37. Matsuoka LY, Ide L, Wortsman J, MacLaughlin J, Holick MF. Sunscreens suppress cutaneous vitamin D_3 synthesis. J Clin Endocrinol Metab. 1987;64:1165–8.

38. Matsuoka LY, Ide L, Wortsman J, Hanifan N, Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D: a preliminary study. Arch Derm. 1988;124:1802–4.

39. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001;22:477–501.

40. Davie M, Lawson DEM. Assessment of plasma 25-hydroxyvitamin D response to ultraviolet irradiation over a controlled area in young and elderly subjects. Clin Sci. 1980;58:235–42.

41. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, DC: National Academy Press; 1999.

42. Chapuy MC, Preziosi P, Maaner M, Arnaud S, Galan P, Hercberg S, Meunier PJ. Prevalence of vitamin D insufficiency in an adult normal population. Osteopor Int. 1997;7:439–43.

43. Thomas KK, Lloyd-Jones DH, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. N Engl J Med. 1998;338:777–83.

44. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med. 2002;112:659–62.

45. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. N Engl J Med. 2001;345:66–7.

46. Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. Osteoporos Int. 1998;8:222–30.

47. Tangpricha V, Koutkia P, Rieke SM, Chen TC, Perez AA, Holick MF. Fortification of orange juice with vitamin D: a novel approach to enhance vitamin D nutritional health. Am J Clin Nutr. 2003;77:1478–83.

48. Trang HM, Cole DEC, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D_3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D_2. Am J Clin Nutr. 1998;68:854–8.

49. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr. 2003;22:142–6.

50. Bengoa JM, Sitrin MD, Meredith S. Intestinal calcium absorption and vitamin D status in chronic cholestatic liver disease. Hepatology. 1984;4:261–5.

51. Lo CW, Paris PW, Clemens TL, Nolan J, Holick MF. Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes Am J Clin Nutr. 1985;42:644–9.

52. Tangpricha V, Turner A, Spina C, Decastro S, Chen T, Holick MF. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. Am J Clin Nutr. 2004;80:1645–9.

53. Holick EA, Lu Z, Holick MT, Chen TC, Sheperd J, Holick MF. Production of previtamin D3 by a mercury arc lamp and a hybrid incandescent/mercury arc lamp. In: Holick, MF, editor. Proceedings of the Biologic Effects of Light, June 16–18, 2001. Boston: Kluwer Academic; 2002. p. 205–12.

54. Aucone BM, Gehrmann WH, Ferguson GW, Chen TC, Holick MF. Comparison of two artificial ultraviolet light sources used for Chuckwalla, *Sauromalus obesus*, husbandry. J Herpetol Med Surg. 2003;13:14–7.

55. Koutkia P, Lu Z, Chen TC, Holick MF. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. Gastroenterology. 2001;121:1485–8.

56. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet. 1998;351:805–6.

57. Apperley FL. The relation of solar radiation to cancer mortality in North America. Cancer Res. 1941;1:191–5.

58. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Oglesby P. Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. Lancet. 1985;9:307–9.

59. Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Preventive Med. 1990;19:614–22.

60. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Cancer. 1992;70:2861–9.

61. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer. 2002;94:1867–75.

62. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and pre-diagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control. 2000;1:847–52.

63. Feldman D, Zhao XY, Krishnan AV. Editorial/mini-review: vitamin D and prostate cancer. Endocrinology. 2000;141:5–9.

64. Chen TC, Holick MF. Vitamin D and prostate cancer prevention and treatment. Trends Endocrinol Metab. 2003;14:423–30.

65. Bikle DD, Nemanic MK, Gee E, Elias P. 1,25-dihydroxyvitamin D3 production by human keratinocytes: kinetics and regulation. J Clin Invest. 1986;78: 557–66.

66. Adams JS, Gacad MA, Anders A, Endres DB, Sharma OP. Biochemical indicators of disordered vitamin D and calcium homeostasis in sarcoidosis. Sarcoidosis. 1986;3:1–6.

67. Schwartz GG, Whitlatch LW, Chen TC, Lokeshwar BL, Holick MF. Human prostate cells synthesize 1,25-dihydroxyvitamin D3 from 25-hydroxyvitamin D3. Cancer Epidemiol. Biomarkers Prev. 1998;7:391–5.

68. Tangpricha V, Flanagan JN, Whitlatch LW, Tseng CC, Chen TC, Holt PR, Lipkin MS, Holick MF. 25-hydroxyvitamin D-1α-hydroxylase in normal and malignant colon tissue. Lancet. 2001;357:1673–4.

69. Cross HS, Bareis P, Hofer H, Bischof MG, Bajna E, Kriwanek S. 25-Hydroxyvitamin D$_3$-1α-hydroxylase and vitamin D receptor gene expression in human colonic mucosa is elevated during early cancerogenesis. Steroids. 2001; 66:287–92.

70. Mawer EB, Hayes ME, Heys SE, Davies M, White A, Stewart MF, Smith GN. Constitutive synthesis of 1,25-dihydroxyvitamin D$_3$ by a human small cell lung cell line. J Clin Endocrinol Metab. 1994;79:554–60.

71. Maas RM, Reus K, Diesel B. Amplification and expression of splice variants of the gene encoding the P450 cytochrome 25-hydroxyvitamin D(3) 1, alpha-hydroxylase (CYP27B1) in human malignant glioma. Clin Cancer Res. 2001;7:868–75.

72. Tsoukas CD, Provvedine DM, Manolagas SC. 125-Dihydroxyvitamin D$_3$, a novel immuno-regulatory hormone. Science. 1984;221:1438–40.

73. Bhalla AK, Clemens T, Amento E, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. J Clin Endrocrinol Metab. 57:1308–10.

74. Mathieu C, Adorini L. The coming of age of 1,25-dihydroxyvitamin D$_3$ analogs as immunomodulatory agents. Trends Mol Med. 2002;8:174–9.

75. Mathieu C, Waer M, Laureys J, Rutgeerts O, Bouillon R. Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D$_3$. Diabetologia. 1994;37:552–8.

76. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxyvitamin D$_3$ reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proc Natl Acad Sci USA. 1996;93:7861–4.

77. Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25-dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. J Nutr. 2000;130:2648–52.

78. Ponsonby AL, McMichael A, van der Mei I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology. 2002; 181–182:71–8.

79. Embry AF, Snowdon LR, Vieth R. Vitamin D and seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. Ann Neurol. 2000;48:271–2.

80. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis. Arthritis Rheum. 2004;50:72–7.

81. Hypponen E, Laara E, Jarvelin M-R, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001;358:1500–3.

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

83. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. Lancet. 1998;352:709–10.

84. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Körfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol. 2003;41:105–12.

85. Fahrleitner A, Dobnig H, Obernosterer A, Pilger E, Leb G, Weber K, Kudlacek S, Obermayer-Pietsch B. Vitamin D deficiency and secondary hyperparathyroidism are common complications in patients with peripheral arterial disease. J Gen Intern Med. 2002;17:663–9.

86. Li Y, Kong J, Wei M, Chen ZF, Liu S, Cao LP. 1,25-dihydroxyvitamin D$_3$ is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002;110:229–38.

v87. Weishaar RE, Simpson RU. Involvement of vitamin D3 with cardiovascular function II: direct and indirect effects. Am J Physiol. 1987;253:E675–83.

88. O'Connell TD, Weishaar RE, Simpson RU. Regulation of myosin isozyme expression by vitamin D$_3$ deficiency and 1,25-dihydroxyvitamin D$_3$ in the rat heart. Endocrinology. 1994;134:899–905.

89. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med. 2003;349:446–56.

90. Bischoff HA, Stahelin HN, Dick W, Akos R, Knecht M, Salis C, Nebiker M, Theiler R, Pfeifer M, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J Bone Min Res. 2003;18:343–51.

91. Bischoff-Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age J Bone Miner Res. 2004;19:265–9.

92. Bischoff-Ferrari HA, Dietrich T, Orav J, Dawson-Hughes B. Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger and older adults. JAMA. 2004;116:634–9.

93. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third national health and nutrition examination survey, 1988–1994. Am J Clin Nutr. 2002;76:187–92.

94. Chapuy MC, Schott AM, Garnero P, Hans D, Delmas PD, Meunier J, Group ES. Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter. J Clin Endocrinol Metab. 1996; 81:1129–33.

95. Chel VGM, Ooms ME, Popp-Snijders C, Pavel S, Schothorst AA, Meulemans CCE, Lips P. Ultraviolet irradiation corrects vitamin D deficiency and suppresses secondary hyperparathyroidism in the elderly. J Bone Miner Res. 1998; 13:1238–42.

96. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Thomesen J, Charles P, Eriksen EF. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. J Intern Med. 2000;247:260–8.

97. Gloth FM, Gundberg CM, Hollis BW, Haddad HG, Tobin JD. Vitamin D deficiency in homebound elderly persons. JAMA. 1995;274:1683–6.

98. Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, et al. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab. 2001;86:1212–21.

99. Sedrani SH, Al-Arabi K, Abanny A, Elidrissy A. Vitamin D status of Saudis: IV. Seasonal variations. Saudi Med J. 1992;13:423–9.

100. Sedrani SH. Low 25-hydroxyvitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. Ann Nutr Metab. 1984;28:181–5.

101. Moore C, Murphy MM, Keast DR, Holick MF. Vitamin D intake in the United States. J Am Diet Assoc. 2004;104:980–3.

102. Chiu KC, Chu A, Go V, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr. 2004;79:820–5.

103. Bell NH, Greene A, Epstein S, Oexmann MJ, Shaw S, Shary J. Evidence for alteration of the vitamin D-endocrine system in blacks. J Pedr. 1985;76:470–3.

104. Kennedy C, Bajdik CD, Willemze R, de Gruijl FR, Bavinck JN. The influence of painful sunburns and lifetime of sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi and skin cancer. J Invest Dermatol. 2003;120:1087–93.

105. Berwick M, Armstrong B, Ben-Porat L, Fine J, Kricker A, Eberle C, Barnhill R. Sun exposure and mortality from melanoma. J Natl Cancer Inst. 2005;97:195–9.

106. Gamgee KML. The artifical light treatment of children. New York: Paul B. Hoeber; 1927.

107. Holick MF, Tian XQ, Allen M. Evolutionary importance for the membrane enhancement of the production of vitamin D3 in the skin of poikilothermic animals. Proc Natl Acad Sci U S A. 92:3124–6.