Special Article

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Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis[1–5]

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ABSTRACT

The purpose of this review is to put into perspective the many health benefits of vitamin D and the role of vitamin D deficiency in increasing the risk of many common and serious diseases, including some common cancers, type 1 diabetes, cardiovascular disease, and osteoporosis. Numerous epidemiologic studies suggest that exposure to sunlight, which enhances the production of vitamin D_3 in the skin, is important in preventing many chronic diseases. Because very few foods naturally contain vitamin D, sunlight supplies most of our vitamin D requirement. 25-Hydroxyvitamin D [25(OH)D] is the metabolite that should be measured in the blood to determine vitamin D status. Vitamin D deficiency is prevalent in infants who are solely breastfed and who do not receive vitamin D supplementation and in adults of all ages who have increased skin pigmentation or who always wear sun protection or limit their outdoor activities. Vitamin D deficiency is often misdiagnosed as fibromyalgia. A new dietary source of vitamin D is orange juice fortified with vitamin D. Studies in both human and animal models add strength to the hypothesis that the unrecognized epidemic of vitamin D deficiency worldwide is a contributing factor of many chronic debilitating diseases. Greater awareness of the insidious consequences of vitamin D deficiency is needed. Annual measurement of serum 25(OH)D is a reasonable approach to monitoring for vitamin D deficiency. The recommended adequate intakes for vitamin D are inadequate, and, in the absence of exposure to sunlight, a minimum of 1000 IU vitamin D/d is required to maintain a healthy concentration of 25(OH)D in the blood. *Am J Clin Nutr* 2004;79:362–71.

KEY WORDS Vitamin D, sunlight, 25-hydroxyvitamin D, cancer, bone health, diabetes

INTRODUCTION

Once our sun ignited, it began to emit enormous amounts of energy. This energy bombarded all of its satellite planets. The third planet from the Sun (ie, Earth) had a huge ocean and a small land mass. In the bubbling, organically rich tide pools, life began to evolve and became dependent on solar energy for its very existence. Early in evolution, organisms captured the sun's energy in the form of carbohydrates through the process of photosynthesis. As organisms evolved, they continued to make a wide variety of complex macromolecules, not only for the purpose of replication but also to sustain life's functions. The life forms took advantage of their ocean environment and became dependent on calcium for signal transduction and metabolic functions. In addition, calcium became an important component for organisms that developed exoskeletons. The use of calcium for structural scaffolding became critically important in the evolution of ocean-dwelling vertebrates. The plentiful calcium in the oceans provided the ideal element to incorporate into a collagen-based matrix that gave rise to the structurally rigid vertebrate skeleton. The development of the vertebrate endoskeleton not only provided an opportunity for organisms to grow in size but also gave organisms the opportunity to venture onto land. As vertebrate organisms left their ocean environment for a land-based existence, they needed to develop an efficient method of utilizing the calcium that was absorbed into plants from the calcium-rich soil environment. Remarkably, it was the sun's energy that was called on to promote the photosynthesis of vitamin D_3 in the skin of vertebrates that was responsible for enhancing the efficiency of intestinal calcium absorption (1).

Little is known about when vitamin D made its appearance on Earth and what its function was. However, it is known that some of the earliest phytoplankton and diatom life forms, including *Emiliania huxlei*, which has existed in the oceans for $>$ 750 million years and which has used calcium for its structural support (it is a coccolithophore), produced ergosterol (provitamin D_2). When exposed to simulated sunlight, the ergosterol in *E huxlei* was converted to previtamin D_2 (which rapidly isomerized to vitamin D_2; 2). *Skeletonema menzelii*, a diatom that also contained ergosterol, converted it to previtamin D_2. Little is known about the biologic function of ergosterol, previtamin D_2, and vitamin D_2 in nonvertebrate species. It has been suggested that ergosterol and its photoproducts are an ideal sunscreening system because of their high absorption of ultraviolet radiation (1). Ergosterol, previtamin D_2, vitamin D_2, and their photoproducts efficiently absorb the ultraviolet radiation that is damaging to

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DNA, RNA, and protein—ie, 230–330 nm. Thus, before the ozone layer (which now efficiently absorbs all ultraviolet radiation < 290 nm) evolved, the ergosterol-vitamin D_2 system may have played a critical role in protecting organisms from the high-energy ultraviolet radiation that could have damaged their ultraviolet-sensitive proteins, RNA, and DNA. It is also possible that, if ergosterol existed in the plasma membrane of early life forms, it altered the membrane's permeability for calcium when it was converted to the structurally less rigid vitamin D_2 (1, 2).

PHOTOSYNTHESIS OF PREVITAMIN D

Ergosterol is a plant and fungal sterol. Animals synthesize cholesterol. The immediate precursor in the cholesterol biosynthetic pathway is 7-dehydrocholesterol (provitamin D_3). 7-Dehydrocholesterol is produced in relatively large quantities in the skin of many vertebrate animals, including humans. The few exceptions are some bat species, mole rats, cats, and dogs (3–5). During exposure to sunlight, the 7-dehydrocholesterol in the epidermal and dermal cells absorbs ultraviolet B (UVB) radiation with wavelengths of 290–315 nm. The absorption of this radiation results in a rearrangement of the 5,7-diene in the B-ring that causes a break in the B-ring to form the 9,10-secosterol, previtamin D_3. Previtamin D_3 is thermodynamically unstable, and it rearranges its double bonds to form the more thermodynamically stable vitamin D_3 structure (**Figure 1**).

Velluz et al (6) were the first to identify previtamin D_3 and to show the transformation of previtamin D_3 to vitamin D_3. At room temperature, this process took ≈12 d to complete (7). Although this transformation was remarkable, it would have been impractical for cold-blooded vertebrates to produce an amount of vitamin D_3 in their skin that was adequate to sustain their calcium-needy skeletons.

Previtamin D_3 exists in 2 conformeric forms. Once 7-dehydrocholesterol undergoes its exocyclic ring opening, it converts to the 5, 6-*cis*, *cis* (cZc) conformer. However, this conformer is extremely unstable because of the steric interference of the C-19 methyl group, and it immediately rotates into the more stable 5, 6-*trans*,*cis* (tZc) previtamin D_3. However, only the cZc conformer can convert to vitamin D_3. To overcome this impediment, the 7-dehydrocholesterol was incorporated into the lipid bilayer of the plasma membrane. This resulted in the sandwiching of 7-dehydrocholesterol between the polar head group and the long-chain fatty acids. Thus, during exposure to sunlight, the 7-dehydrocholesterol immediately converted to cZc previtamin D_3, which could not rotate into the favored tZc conformer, and that resulted in the rapid conversion of previtamin D_3 to vitamin D_3. This probably explains why the conversion of previtamin D_3 to vitamin D_3 in the skin is 10 times faster than that in an organic solvent (7).

FACTORS THAT ALTER PHOTOSYNTHESIS OF PREVITAMIN D_3

During exposure to sunlight, 7-dehydrocholesterol is converted to previtamin D_3, which in turn is isomerized by a thermally induced process to vitamin D_3. Once formed, vitamin D_3, which is structurally incompatible with being sandwiched between the hydrophobic fatty acid chains of the plasma membrane, is ejected into the extracellular space. It is then drawn into the dermal capillary bed by the vitamin D–binding protein, which has a small but effective affinity for it (8).

It is remarkable that lifeguards and sun worshippers have never suffered from vitamin D intoxication due to excessive exposure to the sun (9). The reason for this is that previtamin D_3 and vitamin D_3 efficiently absorb sunlight and are converted to a multitude of other photoproducts, including lumisterol, tachysterol, suprasterols, and toxisterols (1, 2, 9; Figure 1). Thus, because of this unique solar regulation, the skin can never generate quantities of vitamin D_3 excessive enough to cause vitamin D_3 intoxication (9).

Because the production of previtamin D_3 in the skin is directly related to the number of UVB photons that are absorbed by 7-dehydrocholesterol, any process that either decreases the number of UVB photons entering the epidermis or decreases the

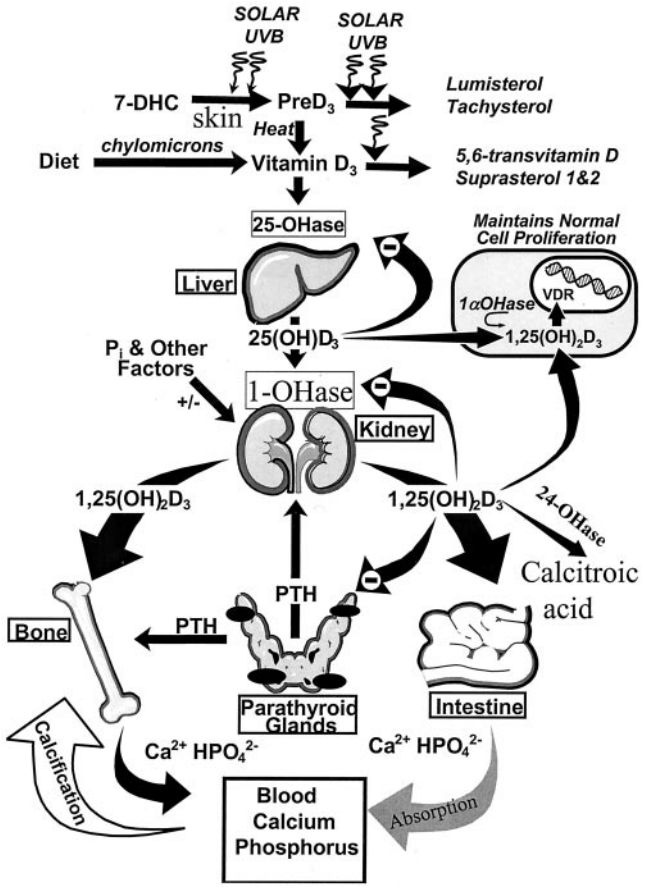

FIGURE 1. Schematic representation of cutaneous production of vitamin D and its metabolism and regulation of calcium homeostasis and cellular growth. During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin absorbs solar ultraviolet B (UVB) radiation and is converted to previtamin D_3 (preD_3). Once formed, preD_3 undergoes thermally induced transformation to vitamin D_3. Further exposure to sunlight converts preD_3 and vitamin D_3 to biologically inert photoproducts. Vitamin D coming from the diet or from the skin enters the circulation and is metabolized in the liver by vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D_3 [25(OH)D_3]. 25(OH)D_3 reenters the circulation and is converted in the kidney by 25-hydroxyvitamin D_3-1α-hydroxylase (1-OHase) to 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$]. A variety of factors, including serum phosphorus (P_i) and parathyroid hormone (PTH), regulate 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$(OH)_2D_3$ also induces its own destruction by enhancing the expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase). 25(OH)D is metabolized in other tissues for the purpose of regulation of cellular growth. VDR, vitamin D receptor.

amount of 7-dehydrocholesterol in the skin will result in a significant reduction in or the complete elimination of vitamin D_3 production in the skin.

A heightened awareness of the role that excessive exposure to sunlight plays in increasing the risk of nonmelanoma skin cancer and wrinkles led to the widespread use of topical sunscreens. Sunscreens efficiently absorb UVB radiation and thus markedly diminish the total number of UVB photons that reach the 7-dehydrocholesterol in the skin's cells. When used properly (ie, 2 mg/cm^2 or 35 mL—ie, 1 oz—on the whole body one time), a sunscreen with an sun protection factor of 8 reduces cutaneous production of previtamin D_3 by $>$ 95% (10, 11). The proper use of a sunscreen with a sun protection factor of 15 reduces the capacity $>$ 99%. The facts that most sunscreen users apply as little as 18% and no more than 35–50% of the recommended amount of sunscreen, and they do tan indicate that they are making sufficient amounts of vitamin D_3 in their skin. The fact that they tan is a reflection of the fact that UVB penetrates the epidermis to stimulate the melanocytes and make vitamin D_3. Melanin is a natural sunscreen that evolved to protect humans from blistering solar radiation as they evolved in equatorial regions of the world. This skin pigment is an extremely effective sunscreen with absorption properties from the ultraviolet C (200–280 nm) into the visible range ($>$ 700 nm), and it competes quite well with 7-dehydrocholesterol for UVB photons. Thus, people of color who have greater amounts of melanin in their epidermis than do whites are less efficient in producing vitamin D_3 than are whites (11, 12). A person with skin type 5/6 (dark skin, never develops a sunburn) requires 10–50 times the exposure to sunlight to produce the same amount of vitamin D_3 in their skin as does a white person with skin type 2 or 3 (12).

The stratospheric ozone layer is efficient in absorbing all solar radiation below 290 nm. However, the ozone layer also can absorb UVB radiation above 290 nm that is responsible for producing previtamin D_3 in the skin. The ultraviolet radiation that can be absorbed by 7-dehydrocholesterol has energies down to 315 nm. Thus, when the angle of the sunlight (zenith angle) reaching the Earth's surface is very oblique (ie, early morning, late afternoon, and winter), sunlight must pass through more ozone, which efficiently absorbs the previtamin D_3–producing UVB photons, and thus very few, if any, reach the earth's surface. Because the zenith angle is dependent on time of day, season of the year, and latitude, those factors have a dramatic effect on the cutaneous production of vitamin D_3 (13, 14). Below $\approx$35°, the zenith angle is more direct, and therefore previtamin D_3 synthesis can occur in the skin year-round. However, above 35° latitude, the angle of the sun is so oblique during the winter months that most, if not all, of the UVB photons below 315 nm are absorbed by the ozone layer, thereby either reducing or completely preventing the production of previtamin D_3 in the skin. For example, residents of Boston (42 °N), Edmonton, Canada (52 °N), and Bergen, Norway (61 °N) cannot produce sufficient quantities of vitamin D_3 in their skin for 4, 5, and 6 mo, respectively. We have conducted studies around the globe that provide guidelines for when, where, and at what time of day vitamin D_3 can be produced in the skin (14; **Figure 2**).

SOURCES OF VITAMIN D

Very few foods naturally contain vitamin D. Cod liver oil and oily fish such as salmon, mackerel, and sardines are good sources. Eating oily fish at least 3–4 times/wk will help satisfy the requirement for adequate intake. Some foods such as milk (100 IU/8 oz), orange juice (100 IU/8 oz), and some cereals and breads are fortified with vitamin D (11, 12, 15). The vitamin D content in milk is often less than the label proclaims it to be, and thus the contribution of vitamin D from the diet is highly variable. To satisfy the body's requirement for vitamin D, most humans obtain it from casual exposure to sunlight. During the spring, summer, and fall, enough vitamin D_3 is produced in the skin to be stored in the body fat, and it can be mobilized during winter months when little, if any, vitamin D_3 is produced in the skin.

The skin has a large capacity to produce vitamin D_3. Blood concentrations of vitamin D_3 were compared in healthy young and middle-aged adults who were exposed to simulated sunlight that was equivalent to being on a sunny beach and obtaining enough sun to cause a slight pinkness to the skin (1 minimal erythemal dose) and who took an oral dose of vitamin D_2. The exposure was equivalent to an oral dose of $\approx$20 000 IU vitamin D_2 (9; **Figure 3**). Although aging decreases the amount of 7-dehydrocholesterol produced in the skin by as much as 75% by the age of 70 y (16, 17), the skin has such a large capacity to make vitamin D_3 that even elderly exposed to sunlight can achieve increased blood concentrations of vitamin D_3 and 25(OH)D (17–19).

CAUSES AND CONSEQUENCES OF VITAMIN D DEFICIENCY

It is estimated that 10 million households in the United States have a reptile as a pet. In their natural environment, reptiles are often exposed to sunlight. They are vertebrates, and, like humans, they require a source of calcium and vitamin D. Iguanas are at particular risk of severe vitamin D deficiency because they are herbivores that, as pets, often are fed a steady diet of lettuce and because they are housed in glass enclosures with a light source that is devoid of UVB transmission. Lettuce contains very little calcium and no vitamin D, and thus iguanas and other vertebrates who do not receive an adequate amount of calcium and vitamin D develop the metabolic bone diseases osteoporosis and osteomalacia that result in fractures and ultimately death. Most reptile owners are aware of the need not only to provide their precious pets with a commercial source of calcium supplementation, but also to provide them with a light that emits UVB radiation similar to sunlight so that the animals can produce vitamin D_3 in their skin.

Humans are no different. They need an adequate source of calcium and vitamin D. Without vitamin D, the small intestine absorbs no more than 10–15% of dietary calcium. In a person with vitamin D sufficiency, the small intestine absorbs, on average, 30% of dietary calcium; during growth, lactation, and pregnancy, the efficiency increases to 80%. Vitamin D deficiency during bone development and growth causes the bone-deforming disease rickets. In adults bone growth stops and bone remodeling continues. Vitamin D deficiency in adults causes secondary hyperparathyroidism that can precipitate and exacerbate osteoporosis (2, 9, 11). The secondary hyperparathyroidism associated with vitamin D deficiency often maintains the serum calcium concentration within the normal range, but it causes a loss of phosphorus in the urine. This loss results in inadequate serum calcium $\times$ phosphorus to promote mineralization of the osteoid in the bone, which in turn results in osteomalacia, ie, nonmineralization of the collagen matrix. Because the nonmineralized matrix cannot provide structural support, the risk of fracture is greater.

How common is vitamin D deficiency? Surprisingly, it has made a resurgence in neonates and young children, in part be-

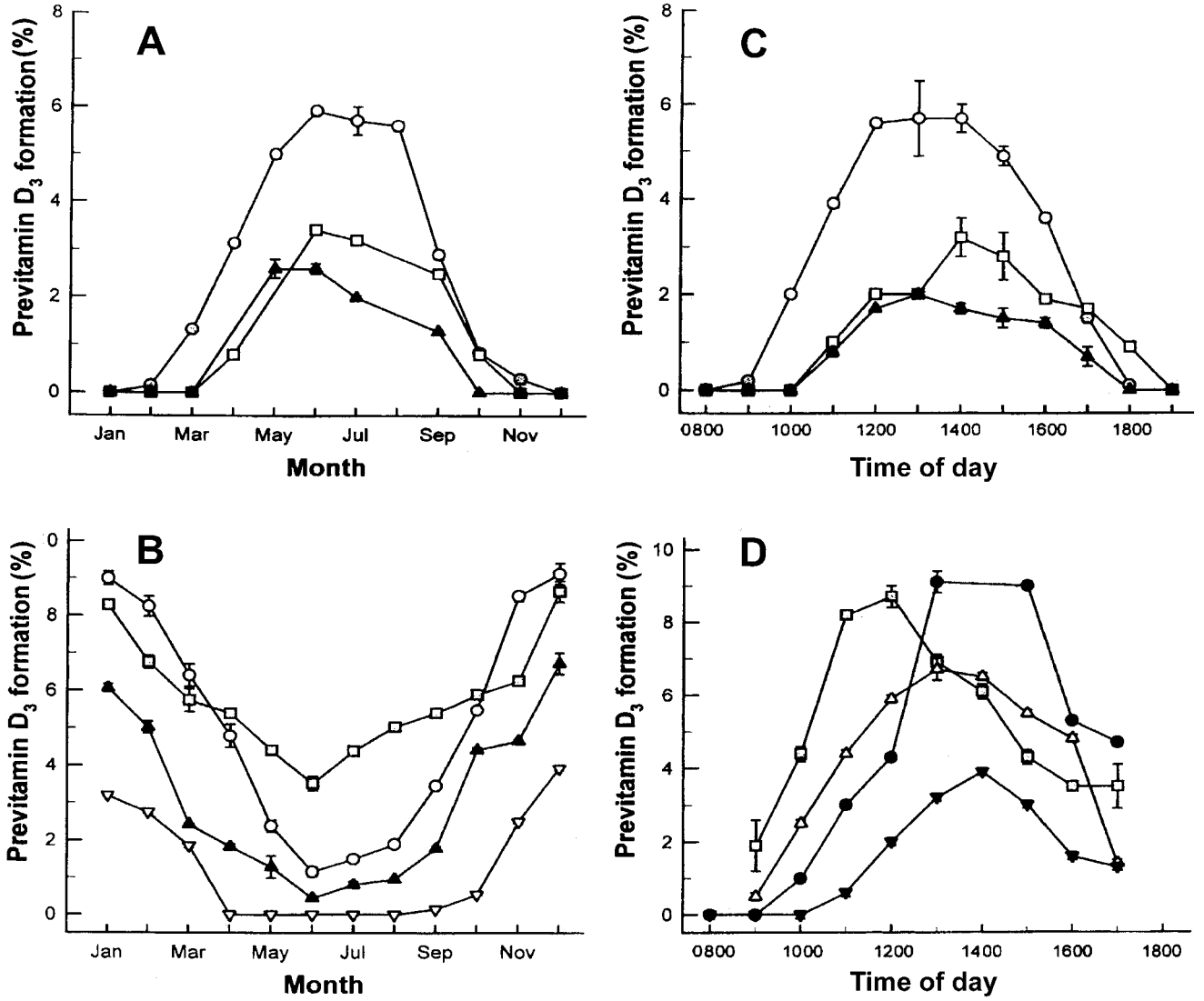

FIGURE 2. Influence of season, time of day, and latitude on the synthesis of previtamin D_3 in the northern (A and C: Boston, ○; Edmonton, □; Bergen, ▲) and southern (B: Buenos Aires, ○; Johannesburg, □; Cape Town, ▲; Ushuala, ▽; D: Buenos Aires, ●; Johannesburg, □; Cape Town, △; Ushuala, ▼) hemispheres. The hour indicated in C and D is the end of the 1-h exposure time in July and January, respectively. Adapted with permission (14).

cause of the campaign to encourage all women to provide all of their infants' nutrition through breastfeeding. Because there is very little, if any, vitamin D in human milk, infants, especially infants of women of color, are at high risk of developing vitaminD deficiency and rickets if they are not given a vitamin D supplement (20, 21).

The elderly are at risk for vitamin D deficiency because of poor dietary vitamin D intake and decreased exposure to sunlight. We observed that 30%, 42%, and 84% of free-living white, Hispanic, and black elderly were vitamin D deficient [25(OH)D < 50 nmol/L] at the end of August in Boston (9). It has always been assumed that young and middle-aged adults are not at risk of vitamin D deficiency because of their outdoor activities and dietary intake. However, it was recently recognized that 42% of African American women aged 15–49 y throughout the United States were vitamin D deficient [25(OH)D < 40 nmol/L] at the end of the winter (22). Hard-working young and middle-aged adults who very seldom spend any time outdoors or always wear sun protection outdoors are also at high risk

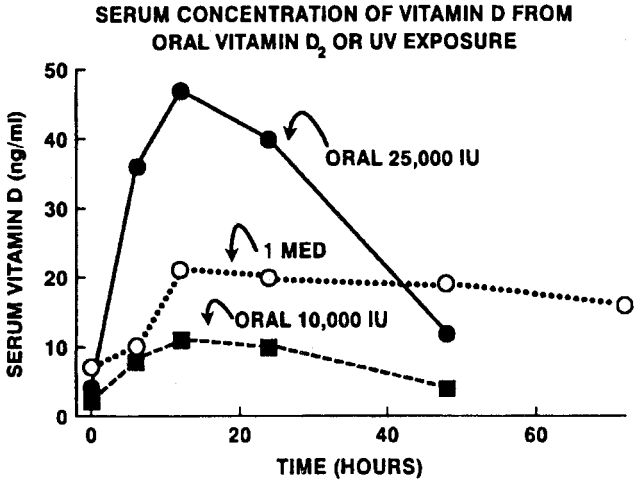

FIGURE 3. Serum vitamin D concentrations after a whole-body exposure to 1 minimal erythemal dose (MED) of simulated sunlight in a tanning bed and after a single oral dose of either 10 000 or 25 000 IU vitamin D_2. UV, ultraviolet. Reproduced with permission (9).

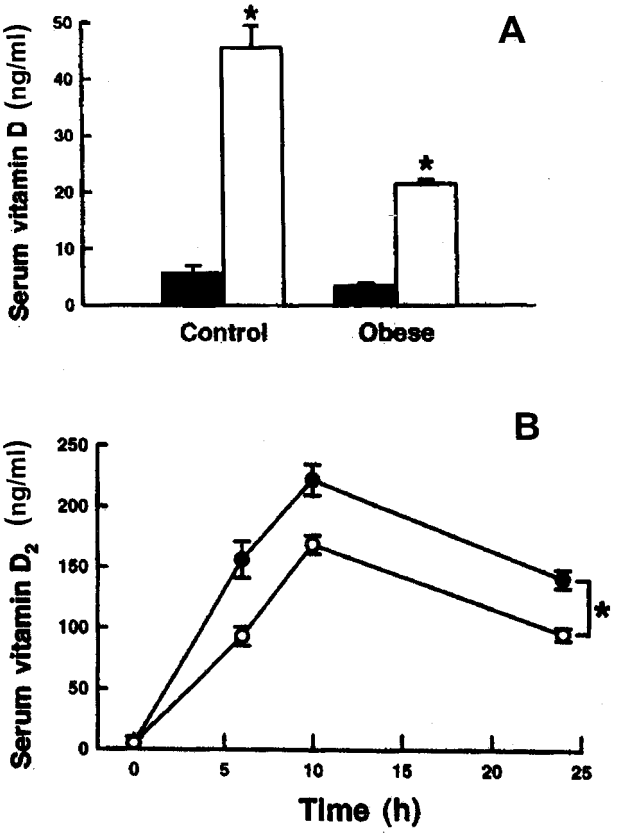

FIGURE 4. A: Mean (± SEM) serum vitamin D_3 concentrations before (■) and 24 h after (□) whole-body irradiation (27 mJ/cm^2) with ultraviolet B radiation. The response of the obese subjects was attenuated when compared with that of the control group. There was a significant time-by-group interaction, $P = 0.003$. *Significantly different from preradiation values ($P < 0.05$). B: Mean (± SEM) serum vitamin D_2 concentrations in the control (●) and obese (○) groups before and 25 h after oral intake of vitamin D_2 (50 000 IU, or 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 (25).

of vitamin D deficiency. We observed that 32% of healthy adults 18–29 y of age were vitamin D deficient [25(OH)D < 50 nmol/L] at the end of the winter in Boston (23).

Obesity is often associated with vitamin D deficiency (24). It is now recognized that, whether vitamin D is ingested in the diet or obtained from exposure to sunlight, it is efficiently deposited in the large body fat stores and is not bioavailable (25; **Figure 4**). This is probably the reason that obese persons are chronically vitamin D deficient.

Vitamin D deficiency often goes undiagnosed or, worse, is misdiagnosed (9, 26–29). There are 3 reasons for this. First, it is believed that either exposure to sunlight or dietary intake of vitamin D is adequate, and, therefore, that Americans and Europeans are not at risk of vitamin D deficiency. Second, physicians who perform routine blood work-ups often obtain a blood calcium value. If they find it to be normal, they assume that the patient is vitamin D sufficient, which is not correct. Third, many physicians erroneously order an analysis for the active form of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], to determine the vitamin D status of a patient. Unfortunately, 1,25$(OH)_2$D not only is not a measure of vitamin D status, but its measurement also can mislead the physician into thinking that the patient is vitamin D sufficient. The reason for this is that, as a person becomes vitamin D-deficient, there is an increase in the concentration of parathyroid hormone (PTH), which increases the renal production of 1,25$(OH)_2$D, the circulating concentrations of which often become normal or even elevated (9).

The vitamin D metabolite that should be measured to determine vitamin D status is 25(OH)D, which is the major circulating form of vitamin D, circulating at 1000 times the concentration of 1,25$(OH)_2$D and having a half-life of ≈2 wk (2, 9, 11). As a person becomes vitamin D-deficient, there is a decrease in the efficiency of intestinal calcium absorption. The ionized calcium concentrations begin to drop; this decrease is immediately recognized by the calcium sensor in the parathyroid glands, which increases the production of PTH (30). PTH compensates for the decrease in intestinal calcium absorption by increasing the mobilization of calcium stores from the skeleton and by increasing tubular reabsorption of calcium in the kidney (31, 32).

NONSKELETAL CONSEQUENCES OF VITAMIN D DEFICIENCY

It has long been recognized that people who live at higher latitudes face an increased risk of many chronic diseases, including common cancers (33–39), multiple sclerosis (39, 40), and hypertension (41). As early as 1941, Apperly (37) observed that people living at higher latitudes, eg, Massachusetts and New Hampshire, had a higher risk of dying of the most common cancers than did people living in the South, eg, Georgia and South Carolina. In 1979, Rostand (41) reported that people living at higher latitudes in both the United States and Europe were at higher risk of hypertension. In the late 1980s and early 1990s, several investigators reported increased risks of dying of colon, prostate, and breast cancer in people living at higher latitudes in both the United States and Europe (33–35). Grant (42) reported that ≥25% of the deaths due to breast cancer in women in Europe could be attributed to the women's lack of UVB from exposure to sunlight. Both men and women are at higher risk of dying of cancer if they have minimum exposure to sunlight (38; **Figure 5**A and B). In a retrospective study, Ahonen et al (44) reported that men on average begin to develop prostate cancer by the age of 52 y, whereas men exposed to more sunlight throughout their lives did not begin developing prostate cancer until 3–5 y later.

VITAMIN D METABOLISM AND NONCALCEMIC FUNCTIONS

It has been known for > 30 y that vitamin D_3 made in the skin or coming from the diet requires 2 obligate hydroxylations, first in the liver and then in the kidney, to create the active form of vitamin D, 1,25$(OH)_2$D (Figure 1). 1,25$(OH)_2$D interacts with its nuclear receptor in the intestine, bone, and kidney to regulate calcium and bone metabolism (9, 31, 45).

Most tissues and cells in the body, including heart, stomach, pancreas, brain, skin, gonads, and activated T and B lymphocytes, have nuclear receptors for 1,25$(OH)_2$D, called vitamin D receptors (46–48). Thus, it is not at all surprising that 1,25$(OH)_2$D has a multitude of biologic effects that are noncalcemic in nature (9, 31, 45).

One of the most intriguing important and unappreciated biologic functions of 1,25$(OH)_2$D is its ability to down-regulate hyperproliferative cell growth (9, 31, 49). Normal and cancer cells that have

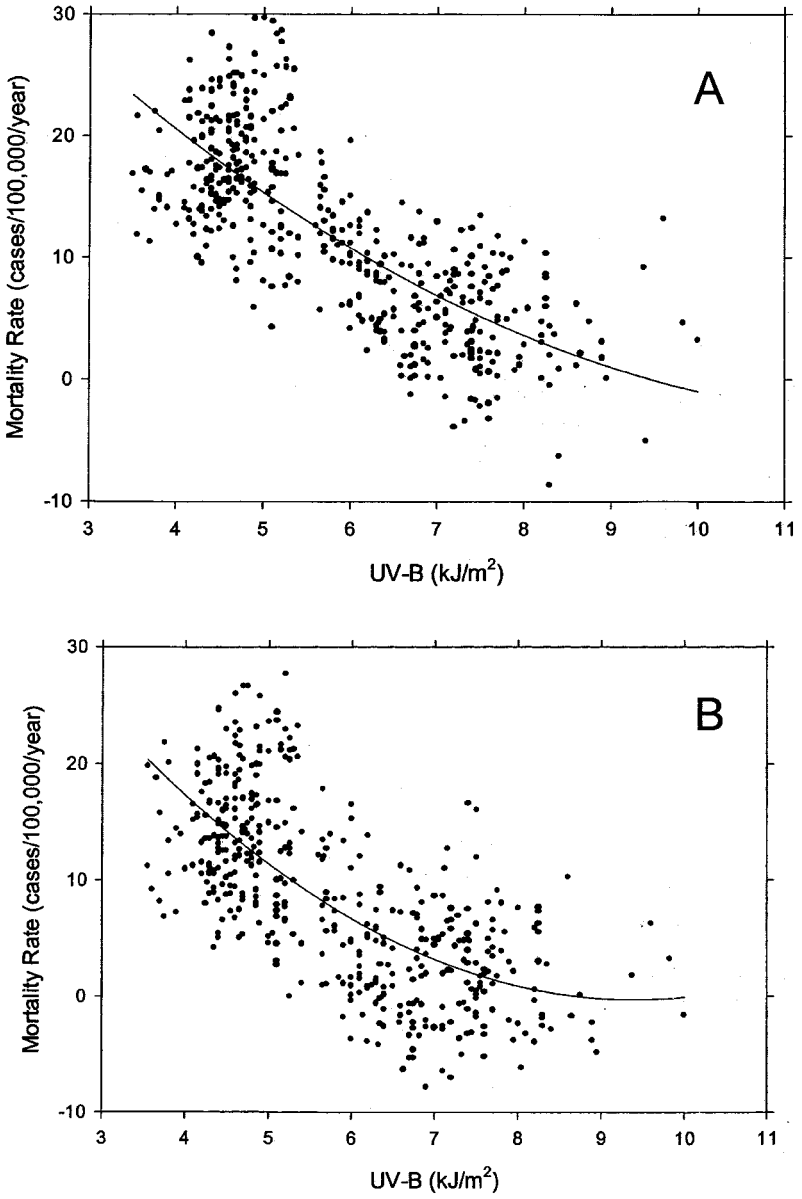

FIGURE 5. A: Premature mortality due to cancer in white females, as determined on the basis of the July 1992 DNA-weighted ultraviolet B (UV-B) radiation by use of a total ozone mapping spectrometer. B: Premature mortality due to cancer in white males in the United States from 1970 through 1994, as determined on the basis of the July 1992 DNA-weighted UV-B radiation. Reproduced by permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc (43). Copyright (2002) American Cancer Society.

a vitamin D receptor often respond to $1,25(OH)_2D$ by decreasing their proliferation and enhancing their maturation. This was the rationale for using $1,25(OH)_2D_3$ and its analogs to treat the common hyperproliferative skin disorder psoriasis (50, 51).

Vitamin D receptors are present in activated T and B lymphocytes and in activated macrophages. The most common autoimmune diseases, including type 1 diabetes, rheumatoid arthritis, and multiple sclerosis, have all been successfully prevented in models using mice that were prone to these diseases if they received $1,25(OH)_2D_3$ early in life (45, 52–55).

When nonobese diabetic mice, who typically develop type 1 diabetes, received $1,25(OH)_2D_3$ throughout their life, their risk of developing type 1 diabetes was reduced by 80% (52, 55). This is in good agreement with the recent observation by Hypponen et al (56) that children receiving 2000 IU vitamin D from age 1 y on decreased their risk of getting type 1 diabetes by 80%.

Krause et al (57) reported that hypertensive patients exposed to UVB radiation for 3 mo had a $>$ 180% increase in circulating concentrations of 25(OH)D and a 6 mm Hg decrease in their diastolic and systolic blood pressures, results similar to those expected if the patients had received a blood pressure medication (**Figure 6**). A similar group of patients who were exposed to ultraviolet A radiation and whose circulating concentrations of 25(OH)D did not increase continued to be hypertensive throughout the 3-mo study. The exact mechanism by which UVB radiation returned the blood pressure to normal [presumably due to

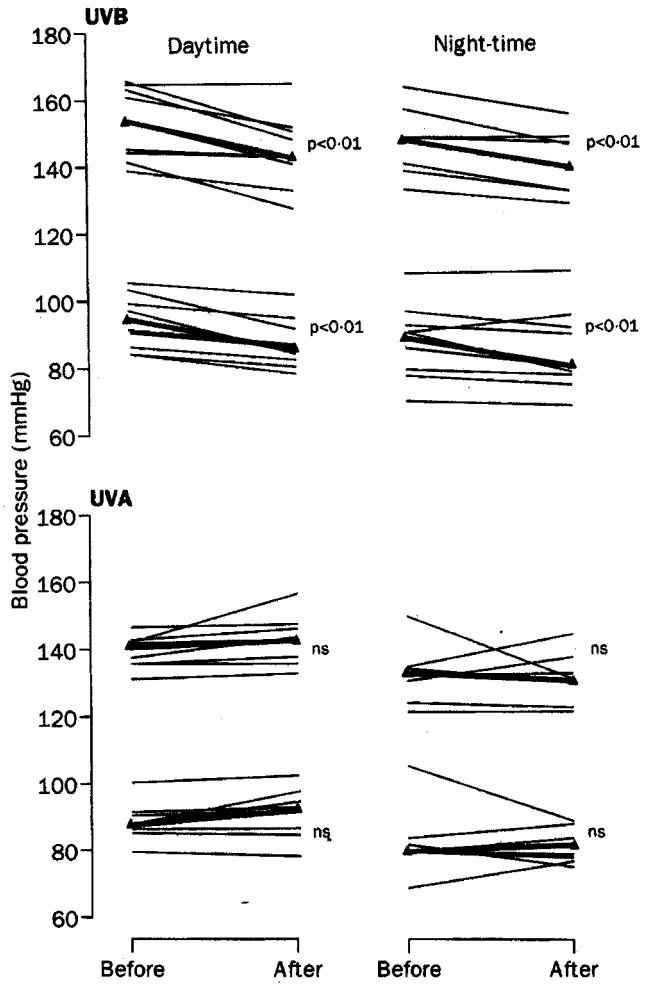

FIGURE 6. Effect of ultraviolet B (UVB) and ultraviolet A (UVA) radiation from a tanning bed on ambulatory daytime and nighttime blood pressure in hypertensive adults before and after exposure to tanning bed radiation 3 times/wk for 3 mo. The daytime and nighttime blood pressures after UVB tanning bed radiation were significantly ($P < 0.01$) different from those before irradiation. The mean is indicated by the thick line. Reproduced with permission from Elsevier (57).

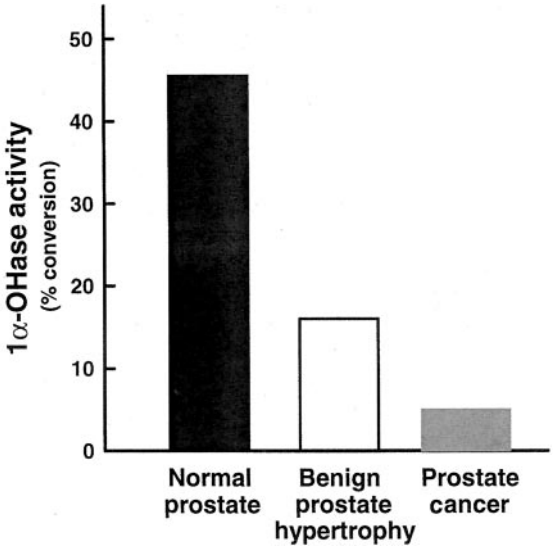

FIGURE 7. Measurement of 25-hydroxyvitamin D-1α-hydroxylase (1α-OHase) activity in prostate cells that were either normal (■), benign but hypertrophied (□), or cancerous (▨). The activity was measured by incubating the cells with [^{3}H]25-hydroxyvitamin D_3 and measuring the percentage of conversion to [^{3}H]1,25-dihydroxyvitamin D_3 after 24 h.

increased blood concentrations of 25(OH)D] in these hypertensive adults is not well understood, but the observation by Li et al (58) sheds some light on the question. They observed in a mouse model that $1,25(OH)_2D$ is effective in down-regulating renin and angiotensin and thereby decreasing blood pressure.

THE CANCER–VITAMIN D CONNECTION

Because an increased risk of vitamin D deficiency is one of the well-documented effects of living at higher latitudes on human health, it was reasonable to suggest that both living at higher latitudes and an increased risk of common diseases were associated with a decrease in the synthesis of vitamin D_3 in the skin. It was intuitively obvious to many, on the basis of new information about vitamin D metabolism and action, that increased exposure to sunlight at lower latitudes would increase blood concentrations of $25(OH)D_3$, which could be activated in the kidney to $1,25(OH)_2D_3$. Because $1,25(OH)_2D_3$ is extremely potent in inhibiting cancer cell growth, this all seemed to make sense. Unfortunately, it was also well known that the renal production of $1,25(OH)_2D$ was tightly regulated by PTH, calcium, and phosphorus (31). Indeed, neither increased exposure to sunlight nor increased oral intake of vitamin D raised blood concentrations of $1,25(OH)_2D$ (59–61). Thus, the question remained: how was it that increased exposure to sunlight was related, presumably by increasing the production of vitamin D_3 in the skin, to a decreased risk of many common cancers and other chronic diseases?

It had always been assumed that the kidney was the sole source for the body's production of $1,25(OH)_2D$. This was based on many observations in animals and in humans whereby, in the absence of any renal function, there were little if any circulating concentrations of $1,25(OH)_2D$. It had been reported that the placenta, epidermal cells, and bone cells could produce $1,25(OH)_2D$, but the physiologic relevance of these observations was not well understood (62, 63). In 1985, Schwartz et al (64) reported that cultured prostate cancer cells expressed the enzymatic machinery to convert 25(OH)D to $1,25(OH)_2D$ (**Figure 7**). Since that observation, it has been shown that a wide variety of normal tissues as well as various cancer cells, including colon cancer, breast cancer, and lung cancer, all have the ability to make $1,25(OH)_2D$ (65–67).

Thus, it is reasonable to conclude that increased exposure to sunlight or increased intake of vitamin D leads to higher circulating concentrations (> 80 nmol/L) of 25(OH)D. 25(OH)D acts as a substrate for the 25-hydroxyvitamin D-1-hydroxylase in various tissues, including colon, breast, and lung. These tissues can produce $1,25(OH)_2D$, which acts in an autocrine fashion to regulate cell growth and decrease proliferative activity (**Figure 8**). It can also induce apoptosis when called on. Thus, $1,25(OH)_2D_3$ can effectively manipulate cell growth and maintain it in a normal proliferative state under most circumstances. Once it accomplishes this, it induces the 25-hydroxyvitamin D-24-hydroyxlase, which hydroxylates the $1,25(OH)_2D$ in the side chain on carbons 23 and 24, and this results in cleavage between carbons 23 and 24 that forms the water-soluble, biologically inert calcitroic acid (31, 68; Figure 1). This is the likely explanation for why patients with renal failure develop a

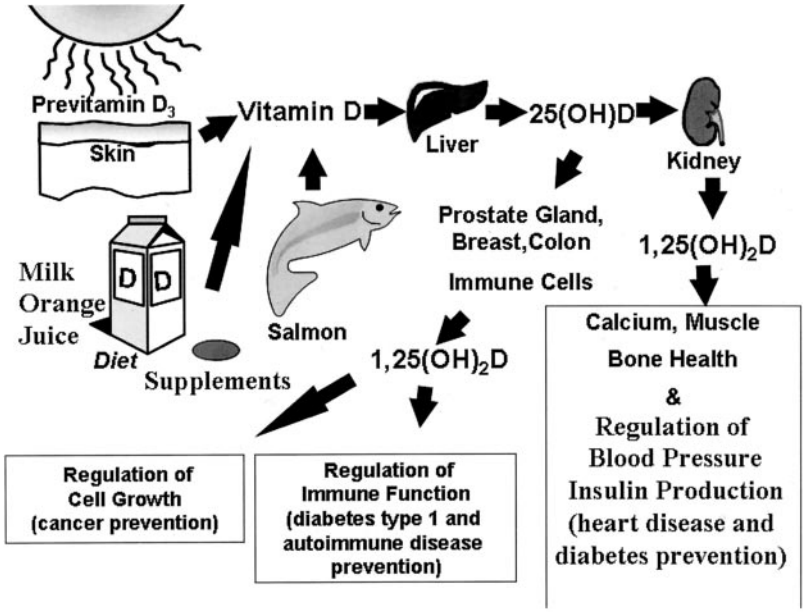

FIGURE 8. Schematic representation of the multitude of other potential physiologic actions of vitamin D with respect to cardiovascular health, cancer prevention, regulation of immune function, and decreased risk of autoimmune diseases. 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D.

$1,25(OH)_2D$ deficiency that results in secondary hyperparathyroidism and renal osteodystrophy.

CONCLUSIONS

The Institute of Medicine reported in 1997 that the recommended vitamin D intake was inadequate for adults over the age of 50 y (69). They recommended that the adequate intake for children and adults up to the age of 50 be 200 IU vitamin D/d. However, adults aged 50–70 y and $\geq$ 70 y required 400 and 600 IU vitamin D/d, respectively. As noted in Heaney's McCollum Award presentation (70) and as indicated in a considerable number of published reports, including that of Heaney et al (71), the new recommendations are totally inadequate, especially if a person has no exposure to sunlight. Without exposure to sunlight, a minimum of 1000 IU vitamin D/d is required. We gave healthy young and middle-aged adults 1000 IU vitamin D/d in orange juice from March through May. Their 25(OH)D concentrations increased by 150%, and what is considered to be a healthy 25(OH)D concentration, ie, 78–100 nmol/L (30–40 ng/mL), was maintained. Those adults receiving orange juice not fortified with vitamin D increased their blood concentration of 25(OH)D by 45%. This was due to their casual exposure to sunlight in the spring (15; **Figure 9**).

The easiest method of correcting vitamin D deficiency is to give the patient one pill that contains 50 000 IU vitamin D once a week for 8 wk (71). This will usually increase the 25(OH)D concentration to $>$ 50 nmol/L (20 ng/mL; **Figure 10**). If not, the vitamin D "tank" may still not be full, and another 8-wk course of therapy usually corrects the vitamin D deficiency (67; Figure 10). One should suspect a fat-malabsorption problem or poor compliance if the 25(OH)D concentration does not increase by $>$ 25% after these treatments. Exposure to sunlight or a tanning bed will correct vitamin D deficiency in patients with severe intestinal fat- malabsorption syndrome (72).

Why should we care about vitamin D deficiency? It is insidious and has both short- and long-term consequences. Infants and young children who are vitamin D deficient may be imprinted for the rest of their lives with increased risks of type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and many common cancers (Figure 8). Adults are at increased risk of common cancers and cardiovascular disease. Recently, it has been reported that

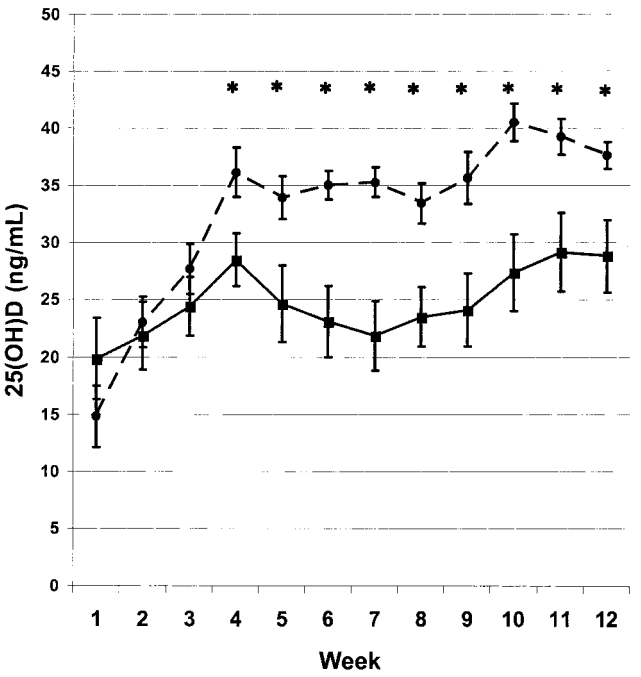

FIGURE 9. Mean (± SEM) weekly 25-hydroxyvitamin D [25(OH)D] concentrations in healthy adults ingesting orange juice fortified with vitamin D (1000 IU · 8 oz^{-1} · d^{-1}, ●) or unfortified orange juice (■). $^{*}P \leq 0.01$. Reproduced with permission (15).

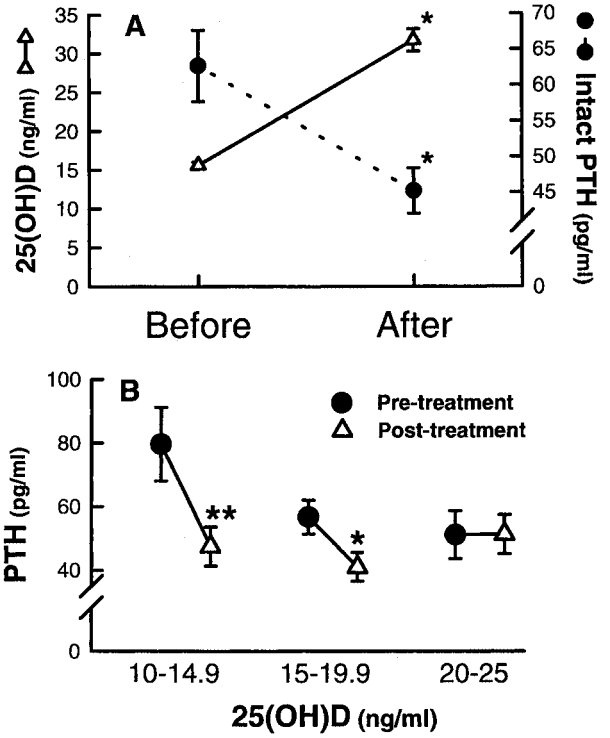

FIGURE 10. A: Serum concentrations of 25-hydroxyvitamin D [25(OH)D; △] and parathyroid hormone (PTH; ●) before and after therapy with 50 000 IU vitamin D_2 and calcium supplementation once a week for 8 wk. $^{*}P < 0.05$. B: Serum concentrations of PTH in patients who had 25(OH)D concentrations between 10 and 25 ng/mL and who were stratified in increments of 5 ng/mL before (●) and after (△) receiving 50 000 IU vitamin D_2 and calcium supplementation for 8 wk. $^{*}P < 0.05$, $^{**}P < 0.01$. Reproduced with permission (71).

young adults with vitamin D deficiency were at greater risk of congestive heart failure than were their vitamin D–sufficient counterparts (73, 74).

Therefore, to maximize health and reduce the risk of common diseases, it is reasonable to pay attention to the 25(OH)D concentration. Just as the blood concentration of cholesterol is often measured on an annual basis, so too should the blood concentration of 25(OH)D be measured. Indeed, vigilance in maintaining a healthy 25(OH)D concentration may have more important health ramifications than a simple lowering of a blood cholesterol concentration to prevent coronary artery disease. A minimum concentration of 25(OH)D should be 50 nmol/L, and, for maximum bone health and prevention of many chronic diseases, the 25(OH)D concentration should be 78–100 nmol/L.

The simplest way to obtain vitamin D is from moderate exposure to sunlight. I recommend that exposure of hands, face and arms, or arms and legs to sunlight for a period equal to 25% of the time that it would take to cause a light pinkness to the skin (1 minimum erythemal dose) is sufficient not only to satisfy the body's requirement, but also to make sufficient amounts of vitamin D to store in the body for use on rainy days and during times when sun exposure is inadequate to produce enough vitamin D in the skin. I have provided guidelines for the amount of sun exposure needed by people of all skin types to achieve their vitamin D requirement without significantly increasing the risk of skin damage and skin cancer (9, 39). Increasing the intakes of foods fortified with vitamin D, including milk, orange juice, cereals, and oily fish, is a reasonable approach to satisfying the body's requirement. Taking >1 multivitamin is counterproductive, because too much vitamin A would be ingested, and that increases the risk of birth defects and osteoporosis. Alternatively, one multivitamin containing 400 IU vitamin D and a vitamin D supplement containing either 400 or 1000 IU vitamin D is appropriate.

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