Sunlight provides most humans with their vitamin D requirement. Adequate vitamin D\textsubscript{3} by synthesis in the skin or from dietary and supplemental sources is essential for bone health throughout life. Vitamin D deficiency is defined as a 25(OH)D concentration <20 ng/mL (50 nmol/L); vitamin D sufficiency as a 25(OH)D >30 ng/mL (75 nmol/L), and insufficiency as 21–29 ng/mL. Vitamin D deficiency and insufficiency has been linked to a wide variety of chronic diseases including common cancers, autoimmune, cardiovascular, and infectious diseases. Healthcare professionals need to be aware of the vitamin D deficiency pandemic. Guidelines for sensible sun exposure and supplemental vitamin D of 800–1000 IU/day are needed.

INTRODUCTION

Prehistorical perspective

Vitamin D is probably one of the oldest hormones, having been in existence for at least 750,000,000 years.\textsuperscript{1,2} Phytoplankton that have lived in the Sargasso sea for more than 750,000,000 years still make ergosterol, which is converted to vitamin D\textsubscript{2} when exposed to sunlight. Although the exact function of vitamin D\textsubscript{2} in these early life forms is not well understood, it is curious that the ultraviolet (UV) absorption spectrum for ergosterol and its photoproducts overlap the UV absorption spectra for the UV-sensitive proteins DNA and RNA\textsuperscript{1,2} (Figure 1). Since 0.1\% of this organism’s dry weight was found to be ergosterol, it is possible that ergosterol served as the first sunscreen to protect these photosynthetic organisms from the damaging effects due to excessive exposure to UV radiation.

As vertebrates evolved in the ocean and left for terra firma approximately 350,000,000 years ago, they took with them their photosynthetic capacity to make vitamin D\textsubscript{3} in their skin. Some evolved into dinosaurs in the Cretaceous period, and required an efficient method to absorb dietary calcium for their massive vertebrate skeletons. It is likely that vitamin D\textsubscript{3} played a critical role in this evolutionary process. When the earth was hit with the massive Chicxulub asteroid 65,000,000 years ago, the cataclysmic fires caused a marked reduction in the amount of sunlight reaching the earth’s surface. This also prevented any vitamin D-producing UV radiation from reaching the earth, causing widespread vitamin D deficiency. Nocturnal rodents that evolved during this time needed minimum, if any, vitamin D, and they survived this cataclysmic event.\textsuperscript{1,3} Thus, vitamin D deficiency may have played a hallmark role in the evolution and prominence of mammals.

Human historical perspective

For humans, the story of vitamin D deficiency and its health consequences were first appreciated with the industrialization of northern Europe. The burning of coal caused severe pollution and the building of housing and industrial structures in close proximity essentially eliminated sun exposure for children, resulting in the bone-deforming disease commonly known as rickets. This disease was caused by sun deprivation and became the scourge of the industrialization of northern Europe and the northeastern United States; by the turn of the 20th century, it was estimated that 80–90\% of children living in Leiden, The Netherlands, and in Boston, USA, suffered from rickets.\textsuperscript{4}
The Viennese physician, Huldschinski, reported in 1919, that children with rickets who were exposed to a mercury arc lamp had marked radiologic improvement in their condition. This was quickly followed by the observation of Hess and Unger in 1921 that rachitic children who were exposed to sunlight showed dramatic healing of their rachitic lesions. This led to the US government’s development of an agency charged with recommending to parents guidelines for sensible sun exposure for their children in order to prevent the scourge of rickets. It was Steenbock who realized that if you could irradiate children and animals to prevent rickets, then you should be able to irradiate food. This resulted in the UV irradiation of cows, their diet, and ultimately their milk to impart antirachitic activity. This led further to the fortification of milk with vitamin D (D represents either D_2 or D_3), which was responsible for the eradication of rickets in the United States and Europe. The unfortunate outbreak of hypercalcemia in Great Britain in the 1950s was thought to be due to intoxicating amounts of vitamin D in the milk and resulted in regulations forbidding the fortification of dairy products with vitamin D throughout Europe.

MECHANISM FOR THE PHOTOPRODUCTION OF VITAMIN D

The immediate precursor of cholesterol is 7-dehydrocholesterol, and its highest concentrations in the human body are found in the skin. The most likely reason for this is that skin exposed to sunlight is the major source of vitamin D_3 for most land vertebrates including humans. During exposure to sunlight, the ultraviolet B (UVB) radiation that is able to penetrate through the earth’s ozone layer with wavelengths between 290 and 315 nm is absorbed by the double bonds in 7-dehydrocholesterol, resulting in the opening of the B ring to form previtamin D_3. This results in a rapid rearrangement of its three double bonds to form vitamin D_3 (Figure 2). Once formed, vitamin D_3 is sterically incompatible with remaining within the plasma membrane and is ejected outward into the extracellular space. Most of the vitamin D_3 production occurs in the epidermis, which is a bloodless tissue. Vitamin D_3 is believed to diffuse from the epidermis into the dermal capillary bed where the vitamin D binding protein quickly binds it for transport to the liver.

People exposed to sunlight every day have never had to be concerned about vitamin D intoxication because once previtamin D_3 and vitamin D_3 are made in the skin they can absorb UVB and UVA radiation, resulting in their conversion to a wide variety of photoproducts that have little, if any, effect on calcium metabolism. This is the likely explanation for why there have been no reported cases of vitamin D intoxication due to excessive exposure to either sunlight or UVB radiation from artificial sources including tanning beds.

SOURCES OF VITAMIN D

Dietary

The major source of vitamin D for most humans has always been exposure to sunlight, however, oily fish, including salmon, is an excellent source of vitamin D that typically contains 500–1000 IU/3.5-ounce serving. However, salmon farmed in the United States receive very little vitamin D in their pelleted diet and have been found to contain just 10–25% of the vitamin D_3 content found in wild-caught salmon. Foods fortified with vitamin D in the United States include milk, orange juice, some breads, margarines, cheeses, and yogurts. In Europe, Sweden, and Finland, milk is fortified with vitamin D_3, but most other European countries still forbid the fortification of dairy products with vitamin D. Other sources include margarine and some cereals. Farmed salmon from Norway...
are fed fish oil, and thus contain a similar amount of vitamin D3 in their flesh as wild-caught salmon. Sun-dried mushrooms are a natural source of vitamin D2. A wide variety of vitamin D supplements is available worldwide.2,4,11–13

Sunlight

During the spring, summer, and fall, enough UVB photons reach the earth’s surface everywhere on the globe for the photosynthesis of vitamin D3 to occur.13,14 However, as the zenith angle of the sun becomes more oblique, the length of the path the UVB photons have to traverse increases. As a result, ozone, which efficiently absorbs UVB radiation, essentially absorbs all of the UVB photons before they reach the earth’s surface. This explains why previtamin D3 production is so variable at different latitudes, times of the day, and seasons,11–16 as dramatically represented in Figure 3. In Boston (42°N), previtamin D3 synthesis begins in March and ends in November. Eighteen degrees north in Bergen, Norway, previtamin D3 synthesis is not detected until April and ends by October. Furthermore, because the zenith angle is more oblique at higher latitudes, there is an approximately 100% difference in the peak levels of previtamin D3 formation in Boston compared to Bergen. In Boston, previtamin D3 production begins in July between 09:00 and 10:00 and ends at approximately 18:00. In Bergen, previtamin D3 synthesis does not begin until around 11:00 and abruptly ends at about 18:00. The difference in peak height between Boston and Bergen is approximately 200% (Figure 3). Thus, although sunlight is present for almost 24 h daily at very high and low latitudes during the
summer, sufficient UVB photons to produce vitamin D$_3$ in the skin is available during only a small portion of that time.

**FACTORS THAT AFFECT CUTANEOUS PREVITAMIN D$_3$ SYNTHESIS**

The aggressive campaign to recommend sunscreen use whenever skin will be exposed to sunlight increases the risk of vitamin D deficiency. The proper application of a sunscreen with a sun protection factor of 15 should absorb 99% of incident UVB photons, resulting in a 99% decrease in production of previtamin D$_3$. Skin pigmentation is also an effective sunscreen. Africans with skin types 5 and 6, i.e., never burn and always tan, have an SPF of approximately 8 to 30. Thus, people of color who live at higher latitudes are at much higher risk of vitamin D deficiency because they often require 5–10 times longer exposure to sunlight compared to Caucasians in order to make the same amount of vitamin D$_3$ in their skin (Figure 4).

Although there has been a lot of debate about how important sunlight is for meeting our vitamin D requirement, a marked seasonal variation in circulating levels of 25-hydroxyvitamin D [25(OH)D] has been well documented in children and adults. One study exposed young adults in bathing suits to simulated sunlight for a period of time causing one minimal erythemal dose (determined by exposing the skin to UV radiation followed 24 h later by evaluating which dose caused a light pinkness, not a sunburn, to the skin); the subjects’ serum vitamin D$_3$ levels were then measured at 12 and 24 h after the exposure. When compared to subjects who received oral doses of vitamin D$_2$, the rise in circulating levels of vitamin D$_3$ was comparable to ingesting between 10,000 and 20,000 IU of vitamin D$_2$ (Figure 5).

Thus, the skin has a large capacity to make vitamin D$_3$. Even though aging significantly decreases the amount of 7-dehydrocholesterol in the skin (i.e., a 70-year-old epidermis has about 25% of the 7-dehydrocholesterol of a 20-year-old epidermis), elderly individuals exposed

---

**Figure 3** Influence of season, time of day in July, and latitude on the synthesis of previtamin D$_3$ in Boston (42°N) –○–, Edmonton (52°N) –□–, and Bergen (60°) –▲–. The hour is the end of the 1-h exposure time in July. Reproduced from Holick © 2007 with permission.

**Figure 4** Change in serum concentrations of vitamin D in (A) two lightly pigmented white (skin type II) and (B) three heavily pigmented black (skin type V) subjects after total-body exposure to 54 mJ/cm$^2$ of UVB radiation. (C) Serial change in circulation vitamin D after re-exposure of one black subject in panel B to a 320 mJ/cm$^2$ dose of UVB radiation. Reproduced from Clemens et al. (1982) with permission from Elsevier.
to UVB radiation from sunlight, a tanning bed, or other UVB-emitting devices effectively raised their blood levels of 25(OH)D.12,23–25

THE VITAMIN D DEFICIENCY PANDEMIC

Vitamin D deficiency is now regarded by most experts to be a 25(OH)D level <20 ng/mL (50 nmol/L).4,11,13,26–30 Since the efficiency of intestinal calcium absorption is enhanced by as much as 65% when osteoporotic women raised their blood levels of 25(OH)D to >30 ng/mL (75 nmol/L)31 and the fact that parathyroid hormone levels begin to level off at their nadir, between 30 and 40 ng/mL28,32 (Figure 6), most experts agree that a 25(OH)D level >30 ng/mL is considered to represent sufficient vitamin D while levels between 21 and 29 ng/mL are insufficient.

Based on these new definitions of vitamin D insufficiency and deficiency, it is estimated that one billion people worldwide are either vitamin D insufficient or deficient. Vitamin D deficiency is highly prevalent in adults over the age of 65 years and in patients with osteoporosis.1,13,26–30,32–36 Numerous studies have reported that vitamin D deficiency is common in postmenopausal women. A cross-sectional observational study conducted at 61 sites across north America revealed that 52% of postmenopausal women receiving an expensive osteoporosis therapy had levels of 25(OH)D <30 ng/mL32 (Figure 6). A multinational study performed in 18 countries in South America, Europe, the Middle East, Asia, and Australia revealed that, overall, 64% of women had a serum level <30 ng/mL.27 Gloth et al.36 reported that 54% of free-living elders in Baltimore, MD, USA, had a 25(OH)D level of <10 ng/mL. A similar study conducted in Boston revealed that 30% of white, 42% of Hispanic, and 84% of African American free-living men and women over the age of 65 had a 25(OH)D level of <20 ng/mL.37

Vitamin D deficiency is also common in children and in young and middle-aged adults. In one study, 36% of otherwise healthy young adults aged 18 to 29 years had a 25(OH)D level of <20 ng/mL at the end of winter, despite the fact that they often took a multivitamin, drank at least one glass of milk a day that was fortified with vitamin D, and ate fish at least once a week.38 Another study showed that 48% of preadolescent white girls living in the US state of Maine had a 25(OH)D level of <20 ng/mL at the end of winter.39 At the end of summer, 17% still had a 25(OH)D level of <20 ng/mL; many of these girls attended summer camp, but they often wore sun protection or avoided direct sun exposure. Gordon et al.40 reported that 54% of adolescent Hispanic and...
black boys and girls had a 25(OH)D level of <20 ng/mL throughout the year. Even children living in Australia,4 Lebanon,41 and India (New Delhi)42 were reported to be at high risk, as were children living in Saudi Arabia and the United Arab Emirates.4,11,43

It had previously been assumed that pregnant women were not at risk of vitamin D deficiency because they often take prenatal vitamins containing 400 IU of vitamin D. However, Lee et al.44 reported that in 40 mother-infant pairs tested at the time of birth, 76% of mothers and 81% of infants had a 25(OH)D level of <20 ng/mL. Seventy percent of the women took their prenatal vitamin containing 400 IU vitamin D, 93% drank on average 2.3 glasses of vitamin D-fortified milk, and 90% ate fish at least once a week. A similar observation was made by Bodnar et al.,45 who found that 29% and 54% of black women had 25(OH)D levels of <15 ng/mL and <30 ng/mL, respectively, at delivery and that 46% of their black neonates were vitamin D deficient. Among the white women in the study, 5% and 42% had <15 and <30 ng/mL, respectively, and 9.7% and 56.4% of their neonates were reported to be vitamin D deficient and insufficient, respectively. Bodnar et al.46 also observed that vitamin D deficiency is associated with preeclampsia.

CONSEQUENCES OF VITAMIN D DEFICIENCY

Vitamin D deficiency and insufficiency result in a decrease in the efficiency of intestinal calcium absorption.31,47 The body is committed to maintaining ionized calcium within the normal physiologic range. It accomplishes this by having the calcium sensor in the parathyroid glands recognizing the ionized calcium.48 A decrease in ionized calcium results in an increase in the expression, production, and secretion of parathyroid hormone (PTH). PTH stimulates the kidneys to produce more 1,25(OH)2D. However, the target tissue levels of 1,25(OH)2D are inadequate in a vitamin D insufficient state; as a result, PTH has two other options to maintain serum calcium levels in a physiologic range. The first is to enhance the tubular reabsorption of calcium in the kidneys. The second is to enhance the mobilization of calcium stores from the skeleton by increasing the expression of RANKL (receptor activator of NFκB) on osteoclasts. This is the signal for preosteoclasts through its RANK interaction with RANKL to stimulate the formation of multinucleated osteoclasts, which release enzymes and hydrochloric acid to dissolve the collagen matrix and release the precious calcium stores into the circulation10,12,47 (Figure 2). The increase in osteoclast activity results in the destruction of the skeleton, which causes osteopenia and osteoporosis and increases risk of fracture.1,13,34,35

Vitamin D deficiency and secondary hyperparathyroidism also result in a mineralization defect of the skeleton that can cause rickets in children and osteomalacia in adults.4,11,13 The major reason for the mineralization defect is that PTH causes excretion of phosphorus into the urine, resulting in a low-normal serum phosphorus level. This results in an inadequate calcium x phosphorus product, which is essential for bone matrix mineralization. On both x-ray and bone densitometry, osteomalacia appears as decreased bone mineral density. Osteomalacia increases the risk of fractures in adults.31,26 In addition, whereas osteoporosis is often a silent disease until a fracture occurs, osteomalacia is often associated with throbbing aching bone pain as well as muscle aches and muscle weakness.11,49,50 These patients who have a normal sedimentation rate are often misdiagnosed as having fibromyalgia, chronic fatigue syndrome, or are simply given the diagnosis of dysthymia.50 Plotnikoff et al.39 reported that among 150 children and adults aged 10–65 years, who presented to an emergency department complaining of nonspecific muscular skeletal aches and pains, 93% were vitamin D deficient; they were initially given a wide variety of diagnoses including degenerative joint disease, dysthymia, fibromyalgia, chronic fatigue syndrome, etc.50

In one 78-year-old gentleman with severe muscle weakness and muscle fasciculations, who was given the diagnosis of amyotrophic lateral sclerosis, all symptoms resolved after his underlying vitamin D deficiency was corrected.51

TREATMENT FOR VITAMIN D DEFICIENCY

Most experts agree that children and adults alike require 800–1000 IU of vitamin D3/d to satisfy the body’s vitamin D requirement.4,11,13,21,29 Sensible sun exposure, which is often limited to no more than 5–15 min of arms and legs between the hours of 10 AM and 3 PM in the spring, summer, and fall at latitudes above and below 35° (and all year near the equator) depending on the time of day, season of the year, latitude, and degree of skin pigmentation is often adequate to satisfy the body’s requirement.4,11,13,16 Because few foods naturally contain vitamin D, it is essentially impossible to satisfy their vitamin D requirement from dietary sources, unless a person eats oily fish 3–5 times a week.

Vitamin D deficiency requires immediate attention and aggressive vitamin D replacement.13,30 When a person is vitamin D deficient, simply giving them what is now thought to be the required amount of vitamin D3, i.e., 1000 IU/day, will only satisfy what the body requires and will gradually increase the blood levels of 25(OH)D. To quickly correct vitamin D deficiency, 50,000 IU of vitamin D2 once a week for 8 weeks is often effective.15,30 In most patients, blood levels of 25(OH)D will rise on
average by 100%. For those who are severely deficient, an additional 8-week course of 50,000 IU of vitamin D2 is recommended. Since the individual presented with vitamin D deficiency, it’s likely that they will become vitamin D deficient again unless they take an adequate amount of vitamin D either as 1000 IU of vitamin D3/d or 50,000 IU of vitamin D twice a month. An alternative strategy that was found to be effective was to give 100,000 IU of vitamin D3 every 3 months.

Patients with intestinal fat malabsorption syndromes often benefit from increasing their vitamin D intake to upwards of 50,000 IU of vitamin D2 two or three times a week. Obese patients sequester vitamin D in the body fat and, therefore, often require more vitamin D to sustain serum levels of 25(OH)D at >30 ng/mL.

VITAMIN D DEFICIENCY AND RISK OF CHRONIC DISEASES

Vitamin D receptor and 1-hydroxylase activity in non-calcium-regulating tissues

It is now recognized that essentially every tissue and cell in the body has a vitamin D receptor (VDR). Studies have suggested that upwards of 200 different genes may be directly or indirectly regulated by 1,25(OH)2D through its VDR. It is also recognized that many tissues and cells in the body are able to express the 25-hydroxyvitamin D-1-hydroxylase (1-OHase; CYP27B1). It has been suggested that raising blood levels of 25(OH)D above 30 ng/mL provides most tissues and cells in the body with enough substrate to permit local production of 1,25(OH)2D. The expression of the 1-OHase has been well documented in human skin, colon, prostate, and activated macrophages, among other tissues and cells. It has also been demonstrated in vitro that cultured normal and malignant breast, colon, and prostate cells metabolize 25(OH)D3 to 1,25(OH)2D3. It has been suggested that local production of 1,25(OH)2D3, which is a potent regulator of cellular proliferation and differentiation and an immunomodulator, is responsible for the many health benefits recently reported as being associated with vitamin D sufficiency (Figure 7).

Vitamin D deficiency cancer link

In 1941 Apperly promoted the concept that living at higher latitudes increased the risk of death due to deadly cancers compared to living at lower latitudes and that exposure to more sunlight increased the risk of non-life-threatening non-melanoma skin cancers. These observations were substantiated by Garland et al., and Hanchette et al., as well as others, who observed that people living at higher latitudes are more likely to develop and die of colon, prostate, ovarian, and breast cancer. Since these initial observations, there have been numerous
studies relating vitamin D deficiency and living at higher latitudes with increased risk of a wide variety of deadly cancers.66 These compelling prospective and retrospective epidemiologic studies have also demonstrated that when 25(OH)D levels are <20 ng/mL, there is a 30–50% increased risk of developing and dying of colorectal, prostate, breast, pancreatic, and several other cancers.11,26,65,66 However, a recent large prospective study known as the Women’s Health Initiative reported that women who received 1000 mg of calcium and 400 IU of vitamin D3/d did not demonstrate any significant change in the risk of developing colorectal cancer, thus raising questions as to whether the previous epidemiologic studies were valid.67 The authors noted, however, that most of the women did not comply in taking their calcium and vitamin D. More importantly, women who had a 25(OH)D level <12 ng/mL and were followed for the next 8 years had a 253% increased risk of developing colorectal cancer.68 The association of increased sun exposure with reduced cancer risk was dramatically demonstrated in Finnish men who worked outdoors; these individuals were found to have a 3–5-year lag time before they developed prostate cancer compared to men who worked indoors.69 Pooled data of 1761 women found that the highest levels of vitamin D consumption correlated with a 50% lower risk of breast cancer, and a study that compared 576 patients with breast cancer to 1135 women without breast cancer found that those who had frequent sun exposure as teenagers or young adults had a 35–40% reduced risk of breast cancer.70,71 Children and adults exposed to the most sunlight were also less likely to develop non-Hodgkin’s lymphoma by as much as 40%.72 Finally, increased sun exposure as children and adults also decreased the risk of dying of malignant melanoma once they developed it.73

Vitamin D deficiency and autoimmune diseases

There is an association with living at higher latitudes and increased risk of many autoimmune diseases including type I diabetes, multiple sclerosis, and Crohn’s disease.11,13,75 Living above 35° latitude for the first 10 years of life has been reported to increase the risk of developing MS by as much as 100%.76 Vitamin D deficiency has been associated with increased risk of developing MS, and women who ingested more than 400 IU of vitamin D/d had a 42% reduced risk of developing MS.77 A similar observation was made in women who ingested more than 400 IU of vitamin D/d; their risk of developing rheumatoid arthritis was reduced by 41%.78

Cardiovascular disease and type II diabetes

Rostand et al.80 reported that living at higher latitudes increases the risk of hypertension. Hypertensive patients exposed to UVB radiation thrice weekly for 3 months and who increased their blood levels of 25(OH)D by approximately 180% had a 6 mmHg decrease in both their systolic and diastolic blood pressures, making them normotensive. Hypertensive patients exposed to UVA radiation under the same circumstances and who did not raise their blood levels of 25(OH)D remained hypertensive throughout the 3-month study.81 1,25(OH)2D is recognized to decrease the production of renin in the kidney as well as to decrease inflammatory factors responsible for chronic heart disease, including C-reactive protein and IL-10.82 Vitamin D deficiency has been associated with increased risk of type II diabetes mellitus, insulin resistance, and decreased insulin production; it has also been associated with metabolic syndrome (syndrome X).83

Mental health

Living at higher latitudes increases the risk of schizophrenia.84 It has been proposed that in utero vitamin D deficiency alters brain development.85 It has also been suggested that vitamin D plays a role in altering serotonin production, which may explain the association with depression and vitamin D deficiency.86

Lung function

Lung function has been related to vitamin D status. Men and women who had a 25(OH)D >35 ng/mL had a 176 cc increase in their forced expiratory volume.87 Children mothers at high risk of vitamin D deficiency in the inner city of Boston were reported to have a higher risk of developing wheezing illnesses.88

Innate immunity

In the 1800s, it was well recognized that cod liver oil was useful in the treatment of Microbacterium tuberculosis.
At the turn of the last century, Finsen reported that exposure to sunlight was effective in the treatment of lupus vulgaris, which is a TB infection of the skin. Patients with TB were often placed in solariums or taken to higher altitudes, both of which seemed to ameliorate and decrease the aggressiveness of the TB infection. It has been known for more than 20 years that activated monocytes and macrophages have 1-OHase activity. However, why these cells made 1,25(OH)₂D was a mystery, since the only obvious consequence was hypercalciuria and hypercalcemia seen in patients who suffer from chronic granulomatosis disorders, including sarcoidosis and TB.

Liu et al. provided convincing evidence that the reason macrophages make 1,25(OH)₂D is to enhance innate immunity. They reported that when the toll-like 2/1 receptor is activated, either by lipopolysaccharide or by a TB tubercle, signal transduction occurs, resulting in increased expression of both 1-OHase and the VDR. 25(OH)D enters the macrophage and is converted to 1,25(OH)₂D. 1,25(OH)₂D then binds to the VDR and enters the nucleus, where it causes an increase in gene transcription for cathelicidin (CD), which is a peptide capable of promoting innate immunity and inducing the destruction of infective agents such as TB. It is also likely that the 1,25(OH)₂D produced in the monocyte/macrophage is released to act locally on activated T (AT) and activated B (AB) lymphocytes, which regulate cytokine and immunoglobulin synthesis, respectively. When 25(OH)D levels are >30 ng/mL, the risk of many common cancers is reduced. It is believed that the local production of 1,25(OH)₂D in the breast, colon, prostate, and other cells regulates a variety of genes that control proliferation, including p21 and p27 as well as genes that inhibit angiogenesis and induce apoptosis. Once 1,25(OH)₂D completes the task of maintaining normal cellular proliferation and differentiation, it induces the 25-hydroxyvitamin D-24-hydroxylase (24-OHase). The 24-OHase enhances the metabolism of 1,25(OH)₂D to calcitriol, which is biologically inert. Thus, the local production of 1,25(OH)₂D does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity and the local production of 1,25(OH)₂D inhibits the expression and synthesis of PTH. The production of 1,25(OH)₂D in the kidney enters the circulation and is able to downregulate renin production in the kidney and to stimulate insulin secretion in the β-islet cells of the pancreas. Reproduced from Holick © 2007 with permission.
**Vitamin D safety and intoxication**

There has been concern that increasing the requirement for vitamin D intake will place both children and adults at increased risk of vitamin D intoxication. However, it should be noted that vitamin D intoxication is extremely rare and is often due to inadvertent or intentional ingestion of excessively high doses of vitamin D. Vieth et al. reported that adult men receiving 10,000 IU of vitamin D3/d for up to 5 months did not experience any untoward toxicity. Most studies suggest that only when more than 10,000 IU of vitamin D3 or D2 is ingested daily for several months to several years will vitamin D intoxication occur, defined by a 25(OH)D level >150 ng/mL, and be associated with hypercalcemia and hyperphosphatemia.

**CONCLUSION**

Vitamin D deficiency is one of the most common undiagnosed medical conditions in the world. Physicians often dismiss the possibility that vitamin D deficiency poses a health risk for their patients. However, the evidence is clear and alarming. Rickets has been resurrected due to the lack of appreciation that human milk contains insufficient vitamin D to satisfy an infant’s requirement, thereby potentially imparting an increased risk of chronic diseases later in life. Fetuses, neonates, and children, as well as young, middle-aged, and older adults are all at high risk of vitamin D deficiency and its insidious health consequences (Figure 7). Vitamin D has evolved into a hormone that is active throughout the body, not only to regulate calcium and bone metabolism, but to control cellular growth, regulate immune function, and control production of insulin and renin among other hormones.

All healthcare professionals should be alert to the vitamin D deficiency pandemic. Measurement of 25(OH)D is recommended. Physicians should never use 1,25(OH)2D as a marker for vitamin D deficiency, since it is often normal or elevated due to secondary hyperparathyroidism.

Recent studies have questioned the role of vitamin D in decreasing risk of fracture and incidence of colorectal cancer. The major problem with these studies is that the community-dwelling subjects who participated in them were less than 60% compliant in taking their calcium and/or vitamin D. In the WHI study, women who took their calcium and vitamin D at least 80% of the time had a statistically significant 29% reduction in hip fracture. More importantly, most of the women in the WHI study were vitamin D deficient at baseline and had increased risk of fracture and colorectal cancer independent of whether they were taking 400 IU of vitamin D, which is only 40% of what is believed to be needed to raise blood levels above 30 ng/mL.

Vitamin D deficiency is a disease caused by sun deprivation. Unfortunately, for the past 30 years, the sun has been demonized by some uninformed dermatology groups; as a result, there has been widespread avoidance of any exposure to sunlight without aggressive sun protection. Guidelines for sensible sun exposure are needed because it is not only one of the most effective ways of guaranteeing vitamin D sufficiency, it is also natural and the most long-lived form of vitamin D. The 30-year campaign of recommending abstinence from sun exposure has not decreased the incidence of non-melanoma skin cancer or melanoma, but it has promoted vitamin D deficiency.

It is clear that the recommended adequate intakes of 200, 400, and 600 IU/day of vitamin D for the 0–50 year, 51–70 year, and 70+ year age groups is woefully inadequate and needs to be increased to at least 800–1000 IU of vitamin D3/d. It is not possible to easily obtain 1000 IU of vitamin D3/d from dietary sources. Excessive exposure to sunlight, especially the number of sunburns is related to increased risk of squamous and basal cell carcinoma. Melanoma is the most dreaded skin cancer for good reason – it is deadly. However, it should be recognized that most melanomas occur on the skin receiving the least sun exposure and several studies have reported that lifetime sun exposure, especially occupational sun exposure, is associated with a reduced risk of developing malignant melanoma. It should also be recognized that children and young adults receiving the greatest exposure to sunlight have a lower risk of dying of malignant melanoma if it should develop.

Thus, there needs to be a reevaluation of the beneficial effect of sensible sun exposure and of increasing the recommended adequate intakes for vitamin D for all age groups. The Australian College of Dermatologists and the Cancer Council for Australia have recommended a balance should be achieved between avoiding increased risk of skin cancer through sun exposure and achieving enough UV radiation to maintain adequate vitamin D levels. This message has been endorsed by the American Cancer Society, the Canadian Cancer Society, the Canadian Dermatological Association, the National Council on Skin Cancer Prevention (US), and the World Health Organization Collaborative Center for the Promotion of Sun Protection. They conclude that in order to minimize the health risk associated with exposure to UVB radiation while maximizing the potential benefits of optimum vitamin D status, supplementation and small amounts of sun exposure are the preferred methods of obtaining adequate vitamin D.
Acknowledgments

Funding. This work was supported in part by NIH grants M01RR00533 and AR36963 and the UV Foundation.

Declaration of interest. MH is a speaker and a consultant for the following companies: Merck, P&G, Amgen, Novartis, and Quest Diagnostics.

REFERENCES


