Sunlight, UV Radiation, Vitamin D, and Skin Cancer: How Much Sunlight Do We Need?

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Michael F. Holick

Abstract

Vitamin D is the sunshine vitamin for good reason. During exposure to sunlight, the ultraviolet B photons enter the skin and photolyze 7-dehydrocholesterol to previtamin D_3 which in turn is isomerized by the body's temperature to vitamin D_3. Most humans have depended on sun for their vitamin D requirement. Skin pigment, sunscreen use, aging, time of day, season, and latitude dramatically affect previtamin D_3 synthesis. Vitamin D deficiency was thought to have been conquered, but it is now recognized that more than 50% of the world's population is at risk for vitamin D deficiency. This deficiency is in part due to the inadequate fortification of foods with vitamin D and the misconception that a healthy diet contains an adequate amount of vitamin D. Vitamin D deficiency causes growth retardation and rickets in children and will precipitate and exacerbate osteopenia, osteoporosis and increase risk of fracture in adults. The vitamin D deficiency pandemic has other serious consequences including increased risk of common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease. There needs to be a renewed appreciation of the beneficial effect of moderate sensible sunlight for providing all humans with their vitamin D requirement for health.

Keywords

Vitamin D · Previtamin D · 25-hydroxyvitamin D · Photobiology · Sunlight · Skin cancer · Vitamin D deficiency · Vitamin D sufficiency · Melanoma · Ultraviolet radiation

Prehistorical Historic Perspective

The major source of vitamin D for most land vertebrates, including humans, comes from exposure to sunlight. From a prehistoric perspective, some of the earliest unicellular organisms that evolved in the oceans including phytoplankton produced vitamin D when exposed to sunlight [1, 2]. Vertebrates that evolved in the ocean took advantage of their high calcium environment and used it effectively for developing a mineralized endoskeleton. When vertebrates ventured onto land, they needed to adapt to the calcium poor environment by increasing their efficiency for intestinal absorption of dietary

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calcium. They took with them the ability to photosynthesize vitamin D_3 in their skin which became essential for enhancing intestinal calcium absorption and maintaining serum calcium levels in most land vertebrates including homosapiens [1, 2].

In the mid-1600s, Whistler and Glissen reported that children living in industrialized cities in Great Britain had short statute and deformities of their skeleton especially their lower legs [3]. This scourge of the industrialization of Europe and North America persisted for more than 250 years. Even though Sniadecki [4] suggested in 1822 that the most likely reason for why his young patients who lived in Warsaw had a high incidence of rickets while the children whom he cared for living in the countryside did not was due to lack of sun exposure. It would take 100 years to appreciate this insightful observation. Palm in 1889 [5] also recognized that "sunbathing" was important for preventing rickets based on reports from his colleagues who saw children living in the most squalid conditions in India and Asia who were not afflicted with rickets whereas it was epidemic in the industrialized cities in Great Britain. By the turn of the twentieth century, upwards of 90% of children living in Leyden, The Netherlands, and in Boston and New York City were afflicted with this bone deforming disease and suffered its long-term consequences. In 1903, Finsen received the Nobel Prize for his insightful observations that exposure to sunlight cured a variety of diseases including lupus vulgaris (skin infected with tuberculosis) [6]. Finally, in 1919, Huldschinski [7] reported that exposure of children to radiation with a mercury arc lamp was an effective means of treating rickets. This quickly followed by the observation of Hess and Unger [8] that exposure of children to sunlight on the roof of a New York City Hospital was an effective means of treating rickets.

The recognition that exposure of both people and animals to ultraviolet radiation was effective in preventing and treating rickets prompted Hess and Weinstock [9] and Steenbock and Black [10] to irradiate with ultraviolet radiation a wide variety of substances including lettuce, grasses and corn, olive and cotton seed oils. Before the irradiation, none of the substances had antirachitic activity, but after the irradiation, they were effective in preventing rickets in rodents. It was also known at that time that cod liver oil was an effective method for preventing and treating rickets, and it was Park [11] who demonstrated that rachitic rats could be cured of their bone disease by either cod liver oil or by ultraviolet irradiation suggesting that the two were related. Steenbock [12] appreciated the practical benefit of these observations when he reported that the irradiation of cow's milk imparted antirachitic activity, and, thus, would be an ideal way of preventing rickets in children.

By the early 1930s, it was appreciated throughout Europe and in the northeastern United States that exposing children to sensible and adequate sunlight without causing sunburn was an effective method of preventing rickets in children. The United States set up an agency in the US Government that promoted sensible sun exposure to parents as a means of preventing their children from developing rickets [3, 13].

Photoproduction of Vitamin D_3

When the skin is exposed to sunlight, the ultraviolet B radiation (UVB) that is able to penetrate through the ozone layer with energies 290–315 nm (Fig. 2.1) is absorbed by 7-dehydrocholesterol in the epidermis and dermis [2, 14, 15]. This absorption causes the double bonds to be excited causing the B-ring to open making the rigid steroid structure into a more flexible molecule known as previtamin D_3 (Fig. 2.2). Previtamin D_3 exists into conformations. It is the thermodynamically less favorable cis, cis form that converts to vitamin D_3. Thus, when previtamin D_3 was made in an isotropic organic solution such as hexane or ethanol, it would take several days for it to convert to vitamin D_3 at 37 ° C. To enhance the thermal-

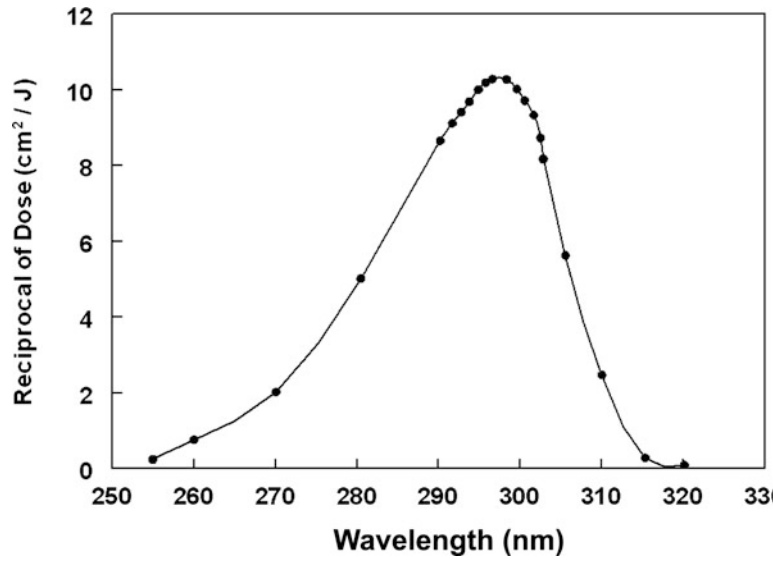

Fig. 2.1 Action spectrum of 7-dehydrocholesterol to previtamin D_3 conversion in human skin. (Holick copyright 2007 with permission)

induced isomerization of previtamin D_3 to vitamin D_3, 7-dehydrocholesterol is incorporated within the fatty acid hydrocarbon side chain and polar head group of the triglycerides in the plasma membrane. When exposed to sunlight, 7-dehydrocholesterol is efficiently converted to the cis, cis conformer which rapidly isomerizes to vitamin D_3 (Fig. 2.2). Vitamin D_3 is ejected out of the plasma membrane into the extracellular space where it enters the dermal capillary bed bound to the vitamin D binding protein [16].

There has been a lot of debate as to whether dietary vitamin D_3 is equivalent to vitamin D_3 made in the skin. Although both have the same biologic activity once they are metabolized, the half-life of vitamin D_3 produced in the skin is prolonged in the circulation in part because 100% is bound to the vitamin D binding protein whereas when vitamin D_3 is ingested, only about 60% is bound to the vitamin D binding protein, and 40% is rapidly cleared in the lipoprotein bound fraction [17]. Other explanations include the additional time it takes for previtamin D_3 to isomerize to vitamin D_3 and the slow gradual diffusion of the vitamin D_3 from the epidermis into the dermal capillary bed.

Factors Controlling Cutaneous Vitamin D Synthesis

Melanin evolved as a sunscreen that absorbed UVB and ultraviolet A (390–400 nm) radiation protecting the UV absorbing macromolecules including DNA, RNA, and proteins from the damaging effects from excessive exposure to UVR. However, as people migrated north and south of the equator, they needed to quickly mutate their skin pigment gene in order to have the ability to make enough vitamin D to sustain their calcium and bone metabolism [18]. This is supported by the observation that Neanderthals had a mutation of their melanocyte-stimulating hormone receptor resulting in them being red-headed and having Celtic-like fair skin which would have facilitated the production of vitamin D3 when they migrated into Europe [19].

Melanin is so efficient in absorbing UVB radiation that it markedly reduces the cutaneous photosynthesis of vitamin D_3. The dark melanin pigment of Africans and African Americans with skin types 5 and 6 (never burns, always tans) is so efficient in absorbing UVB radiation that it reduces the capacity of the skin to produce

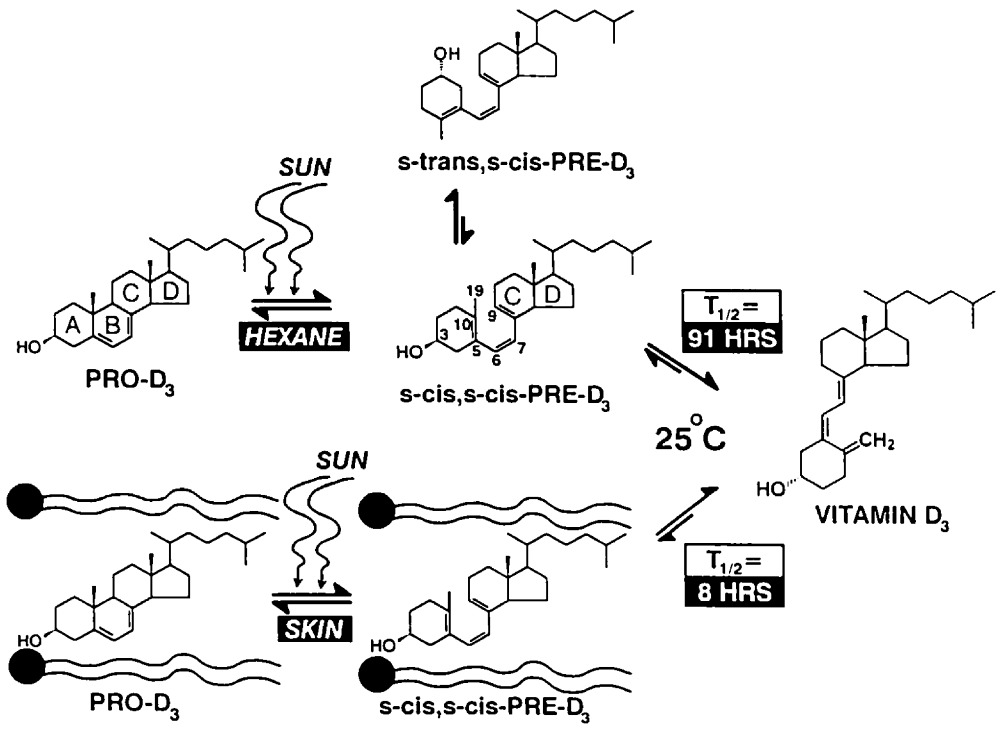

Fig. 2.2 Photolysis of provitamin D_3 (pro-D_3; 7-dehydrocholesterol) into previtamin D_3 (pre-D_3) and its thermal isomerization to vitamin D_3 in hexane and in lizard skin. In hexane is pro-D_3 photolyzed to *s-cis,s-cis*-pre-D_3. Once formed, this energetically unstable conformation undergoes a conformational change to the *s-trans*, *s-cis*-pre-D_3. Only the *s-cis,s-cis*-pre-D_3 can undergo thermal isomerization to vitamin D_3. 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 vitamin D_3. (Holick copyright 2013 with permission)

previtamin D_3 by 95–99% when compared to a Caucasian with skin type 2 (always burns, sometimes tans) [20].

The application of a sunscreen with a sun protection factor of 30 absorbs approximately 97.5% of UVB radiation, and, thus, reduces the skin's capacity to produce previtamin D_3 by 97.5% [21]. The angle at which the sun's rays hit the earth's surface has a dramatic effect on the cutaneous production of previtamin D_3. As the angle of the sun becomes more oblique to the earth's surface, the UVB photons have to travel a longer path through ozone which efficiently absorbs them. Thus, season, latitude, time of day as well as weather conditions dramatically affect the cutaneous production of previtamin D_3 [22] (Fig. 2.3). Living above and below approximately 35° latitude, children and adults are able to produce an adequate amount of vitamin D_3 in their skin during the spring, summer, and fall. However, essentially all of the UVB photons are absorbed during the winter months, thus, either completely eliminating or markedly reducing the capacity of the skin to produce vitamin D_3. This is the explanation for why there is a seasonal variation in circulating levels of 25-hydroxyvitamin D_3 [25(OH)D] which is considered to be the major circulating form of vitamin D [23–25] (Fig. 2.4). Similarly, early in the morning and late in the afternoon, the sun's rays are more oblique, and as a result, most of if not all of the UVB photons are absorbed by the ozone layer.

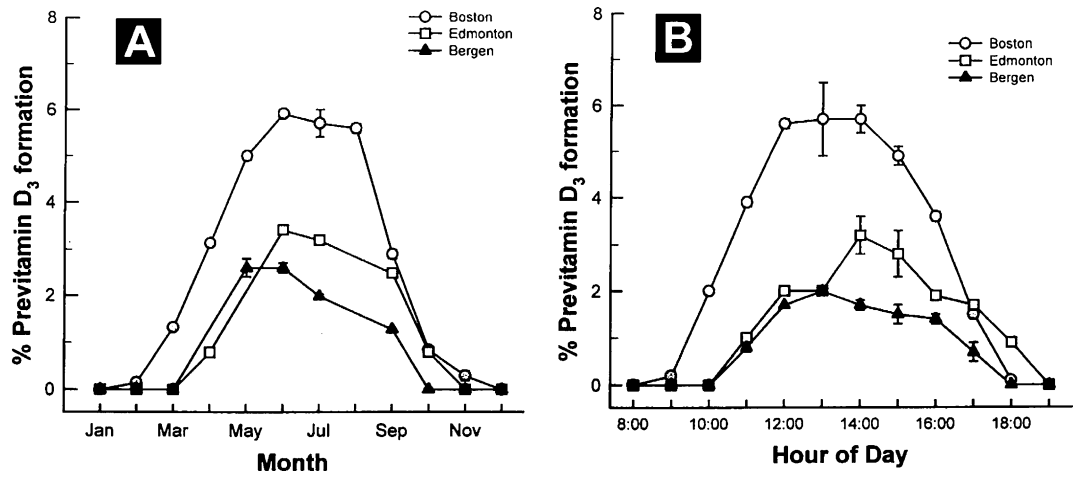

Fig. 2.3 Influence of season, time of day in July, and latitude on the synthesis of previtamin D_3 in Boston (42°N) -○-, Edmonton (52°N) -□-, Bergen (60°) -▲-. The hour is the end of the 1 h exposure time in July. (Holick copyright 2007 with permission)

Thus, even in the summer in the early morning and late afternoon, little, if any, vitamin D_3 is produced in the skin (Fig. 2.3).

Sources and Metabolism of Vitamin D

The major source of vitamin D (D represents D_2 or D_3) for most humans is exposure to sunlight. Very few foods naturally contain vitamin D. These include oily fish such as salmon, cod liver oil which contains vitamin D_3 and sun-dried mushrooms which contains vitamin D_2 [25]. Although it was thought that vitamin D_3 was 2–3 times more effective in raising blood levels of 25(OH)D compared to the same dose of vitamin D_2, a recent study found that physiologic doses of vitamin D_2 are equally as effective as vitamin D_3 not only in maintaining circulating levels of 25(OH)D but also circulating levels of the active form 1,25-dihydroxyvitamin D [1,25 (OH) $_2$D] [26]. Some foods are fortified with vitamin D including milk and some juice products in the United States and Canada, and some breads, margarines, and cereals in the United States, Canada, and Europe. Sweden and Finland fortify milk with vitamin D_3 and India now permits the fortification of milk and cooking oil with vitamin D_2 [26]. Typically there is 100 IU (10 micrograms) of vitamin D in a serving such as 8 ounces of milk or orange juice [25].

Once vitamin D is made in the skin or ingested from the diet, it must be metabolized in the liver to 25(OH)D [24, 25, 28] (Fig. 2.5). The metabolite is biologically inactive, however, it is the major circulating form of vitamin D that is used by physicians to determine a patient's vitamin D status. 25(OH)D undergoes an obligate hydroxylation by the 25-hydroxyvitamin D-1-α-hydroxylase (CYP27B1; 1-OHase) in the kidneys to form the biologically active form $1,25(OH)_2D$. $1,25(OH)_2D$, a steroid-like hormone, interacts with its nuclear vitamin D receptor (VDR) in target tissues including the small intestine, osteoblasts in bone, and in the renal tubular cells in the kidneys. $1,25(OH)_2D$ is responsible for the maintenance of calcium and phosphate homeostasis and bone health by increasing the efficiency of intestinal calcium and phosphate absorption, stimulating osteoblast function and increase bone calcium resorption. It also enhances the tubular resorption of calcium in the kidneys [24, 25, 28] (Fig. 2.5).

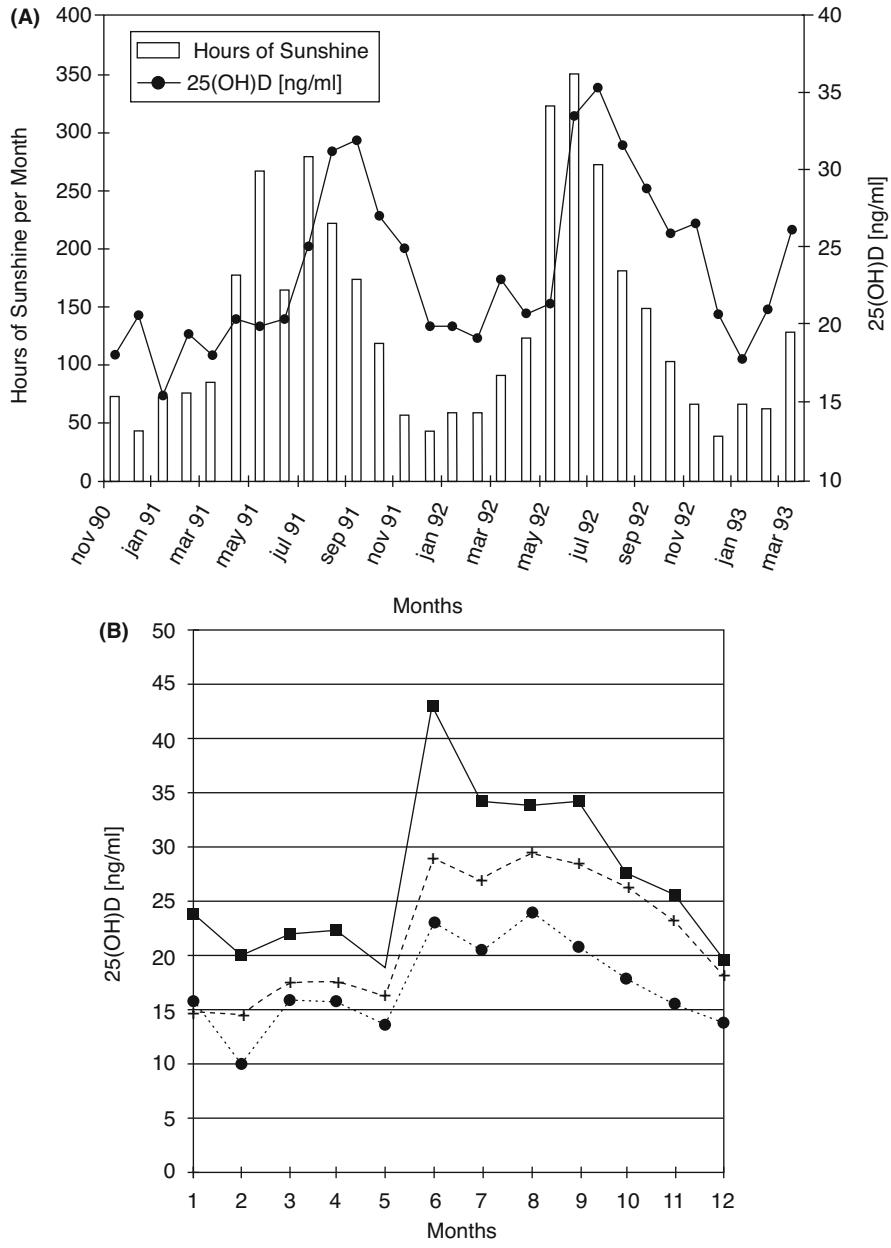

Fig. 2.4 (**a**) Relationship between hours of sunshine and serum 25(OH)D. ■ Hours of sunshine; ● 25(OH)D (ng/ml). (**b**) Seasonal fluctuation of serum 25(OH)D according to frequency of sun exposure. ■ Regular sun exposure; ◆ Occasional sun exposure; ● Avoiding direct sun exposure. (Holick copyright 2013)

$1,25(OH)_2D$ is such a potent regulator of calcium metabolism that in order to control its own actions, it induces its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) [24, 25, 28]. CYP24A1 causes oxidation on carbons 24 and 23 leading to the formation of a C23 acid known as calcitroic acid. This water-soluble inactive metabolite is excreted in the bile (Fig. 2.5).

Role of Vitamin D in the Prevention of Chronic Diseases

Most tissues and cells in the body including brain, skin, breast, prostate, colon, and activated T and B lymphocytes possess a VDR [24, 25, 28–31]. It is now recognized that $1,25(OH)_2D$ is one of the most potent hormones for regulating cell growth and maturation. It is estimated that more than 2000 genes are either directly or indirectly influenced by $1,25(OH)_2D$ [30–32].

There have been numerous studies that have implicated living at higher latitudes and being at increased risk of vitamin D deficiency with many serious and chronic and deadly diseases including cancers of the colon, prostate and breast, autoimmune diseases including multiple sclerosis, type I diabetes and rheumatoid arthritis, infectious diseases including tuberculosis and influenza and hypertension and heart disease [24, 25, 28–50].

What has been perplexing is the fact that exposure to sunlight results in an increase of circulating levels of 25(OH)D but not $1,25(OH)_2D$. The reason is that parathyroid hormone, calcium and phosphorus and fiberblast growth factor 23 tightly control the production of $1,25(OH)_2D$ in the kidneys [25, 28] (Fig. 2.5). Since 25(OH)D is incapable of altering vitamin D responsive gene expression at physiologic concentrations, there needed to be another explanation for the sunlight-vitamin D health connection.

It has been recognized for more than 30 years that activated macrophages, placenta, and skin expressed the 1-OHase [24, 25, 51–59]. In the late 1990s, there were numerous reports of various cell culture systems that expressed the 1-OHase that were capable of converting $25(OH)D_3$ to $1,25(OH)_2D_3$ including colon, prostate, breast, and lung cell cultures [53–57]. It was also observed that normal prostate cells obtained from prostate biopsies and both normal and colon cancer cells obtained at the time of surgery expressed the 1-OHase and had the capacity to make $1,25(OH)_2D$ [54]. These observations have led to the hypothesis that by raising blood levels of 25(OH)D, there is enough substrate for many tissues and cells in the body that express the 1-OHase to produce locally $1,25(OH)_2D$. It is believed that the local production of $1,25(OH)_2D$ is important for regulating cell growth and maturation, and, thus, is able to prevent cells from becoming malignant. $1,25(OH)_2D_3$ accomplishes this by either restoring the cell to its normal proliferative state or by inducing its death by apoptosis. If the cell becomes malignant, an additional strategy for $1,25(OH)_2D$ is to inhibit angiogenesis to the malignant cells [58].

$1,25(OH)_2D$ locally produced by macrophages is important for innate immunity in humans. $1,25(OH)_2D$ enhances the production of the bacteriocidal protein cathelicidin which was shown to be ineffective in killing effective agents including Microbacterium tuberculosis [48]. $1,25(OH)_2D$ is also an effective immunomodulator which may be the explanation for why the local production of $1,25(OH)_2D$ by activated macrophages that is released locally and paracrine fashion to modulate lymphocyte activity [25] may be important for reducing the risk of developing multiple sclerosis, rheumatoid arthritis, and Crohn's disease (Fig. 2.5) [25, 28]. In addition, $1,25(OH)_2D$ enhances the production of insulin, and, thus, may play an important role in type II diabetes [59] and metabolic syndrome [60] and inhibits the production of renin [61] which is important for blood pressure regulation.

Vitamin D Deficiency Pandemic

It is estimated that one billion people worldwide are at risk of vitamin D deficiency [25]. Upwards of 30–50% of both children and adults in the United States, Europe, South America, Middle East, and Far East are at risk [24–28, 62–77]. The major cause for this pandemic is the lack of appreciation of the beneficial effect of sunlight in producing vitamin D [24, 28]. In the sunniest areas of the world, vitamin D deficiency is common because of lack of adequate sun exposure [27, 73–75].

It has been previously thought that the adequate intake for vitamin D to satisfy the body's

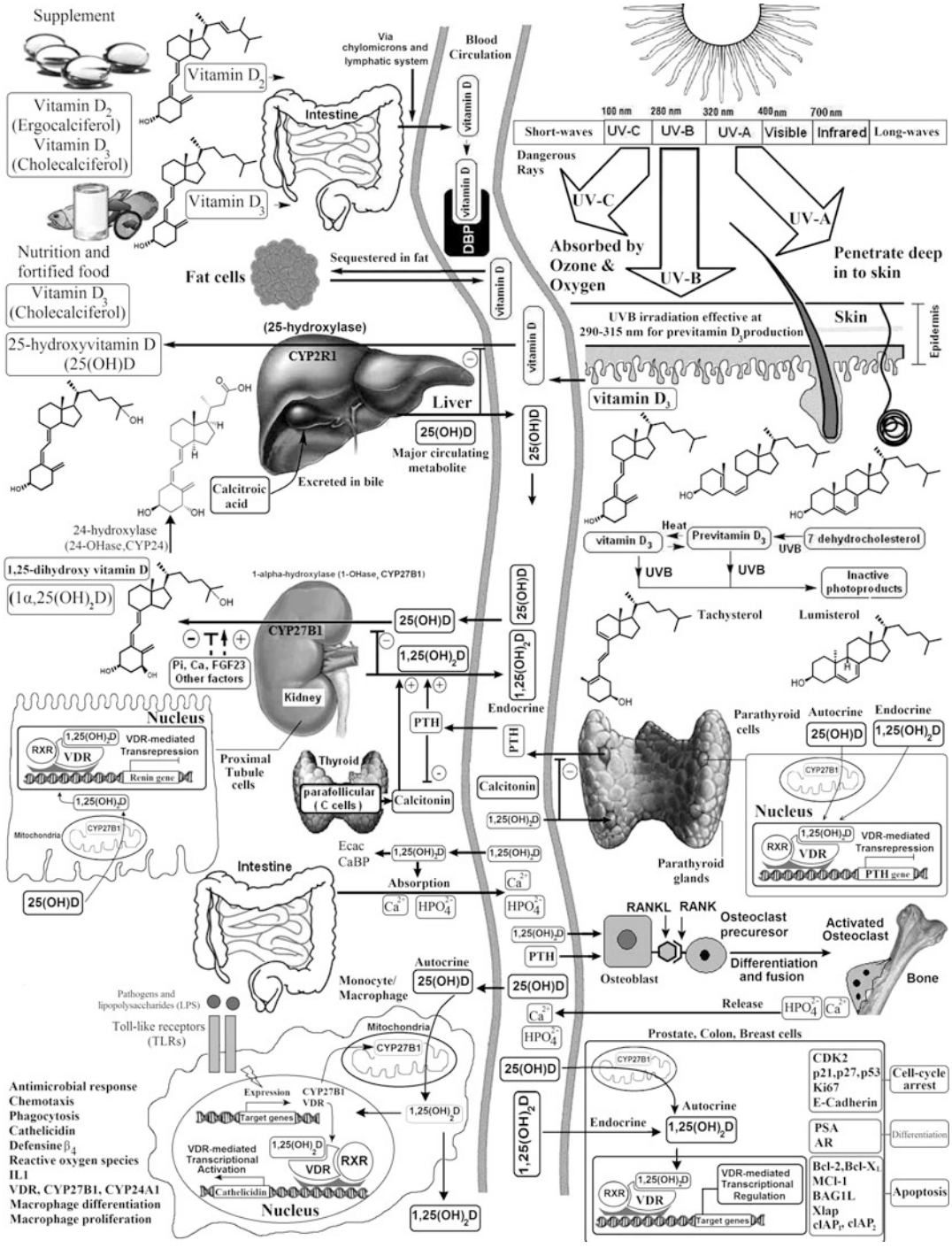

Fig. 2.5 Schematic representation of the synthesis and metabolism of vitamin D for skeletal and non-skeletal function. During exposure to sunlight, 7-dehydrocholesterol in the skin is converted to previtamin D_3. Previtamin D_3 immediately converts by a heat-dependent process to vitamin D_3. Excessive exposure to sunlight degrades previtamin D_3 and vitamin D3 into inactive photoproducts. Vitamin D_2 and vitamin D_3 from dietary sources are incorporated into chylomicrons, transported by the lymphatic system into the venous circulation. Vitamin D (D represents D_2 or D_3) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D-binding protein(DBP), which transports it to the liver, where vitamin D is converted by the vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by

requirement was 200 IU for all children and adults up to the age of 50 years, 400 IU for adults 51–70 years, and 600 IU of vitamin D for adults over the age of 70 [78]. In 2010 the Institute of Medicine (IOM; National Academy of Medicine) recommended that infants, children, adults up to the age of 70, and adults over the age of 70 required 400, 600, 600, and 800 IUs of vitamin D daily respectively [79]. After a careful review of the literature the committee for the Endocrine Society's Practice Guidelines on Vitamin D recommended that to treat and prevent vitamin D deficiency infants should receive 400–1000 IUs daily, children 1 year and older 600–1000 IUs daily, and adults 1500–2000 IUs daily. For obese adults the recommendation was to increase intake by two to threefold because vitamin D is fat soluble and is diluted in the body fat and less bioavailable [67]. The IOM defined vitamin D deficiency, insufficiency and sufficiency with the measurement of serum 25 (OH)D of <12 ng/mL, 12–19 ng/mL, and 20 and greater ng/mL respectively [79]. The Endocrine Society recommended that vitamin D deficiency, insufficiency, and sufficiency for maximum bone health should relate to blood levels of 25(OH)D of >20 ng/mL, 21–29 ng/mL, and 30–100 ng/mL respectively. In addition, The Endocrine Society considered the UL (upper level causing no harm) for vitamin D for infants, children, and adults to

Fig. 2.5 (continued) clinicians to measure vitamin D status (although most reference laboratories report the normal range to be 20–100 ng/ml, the preferred healthful range is 30–60 ng/ml). It is biologically inactive and must be converted in the kidneys by the 25-hydroxyvitamin D-1a-hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. $1,25(OH)_2D_3$ is then taken up by target cells and targeted to intracellular D-binding proteins (IDBP) to mitochondrial 24-hydroxylase or to the vitamin D receptor (VDR). The $1,25(OH)_2D_3$-VDR complex heterodimerizes with the retinoic acid receptor (RXR) and binds to specific sequences in the promoter regions of the target gene. The DNA bound heterodimer attracts components of the RNA polymerase II complex and nuclear transcription regulators. Serum phosphorus, calcium fibroblast growth factors (FGF-23), and other factors can either increase or decrease the renal production of 1,25(OH)2D. $1,25(OH)_2D$ feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. $1,25(OH)_2D$ increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize $1,25(OH)_2D$ to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. $1,25(OH)_2D$ enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel (ECaC) and the calbindin 9 K (calcium-binding protein, CaBP). $1,25(OH)_2D$ is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of the NF-kB ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL, which induces the preosteoclast to become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote the mineralization of the skeleton. Autocrine metabolism of 25(OH)D; when a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as Mycobacterium tuberculosis or its lipopolysaccharide, the signal upregulates the expression of VDR and 1-OHase. A 25(OH)D level of 30 ng/ml or higher provides adequate substrate for 1-OHase to convert 25(OH)D to $1,25(OH)_2D$ in mitochondria. $1,25(OH)_2D$ travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as M. tuberculosis. It is also likely that the $1,25(OH)_2D$ produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. When the 25(OH)D level is approximately 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 tissues regulates a variety of genes that control proliferation, including p21 and p27, as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. Once $1,25(OH)_2D$ completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 24-OHase, which enhances the catabolism of $1,25(OH)_2D$ to the biologically inert calcitroic acid. Thus, locally produced (autocrine) $1,25(OH)_2D$ 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 parathyroid hormone. The $1,25(OH)_2D$ produced in the kidney enters the circulation and can downregulate rennin production in the kidney and stimulate insulin secretion in the beta islet cells of the pancreas. (Holick copyright 2013 with permission)

be 1000, 2000, and 10,000 IUs daily [67]. There has been concern about vitamin D toxicity which can cause hypercalcemia and hyperphosphatemia resulting in cardiovascular calcification and nephrocalcinosis. Vitamin D toxicity is one of the rarest medical conditions and is caused by intentional or accidental ingestion of huge amounts of vitamin D for a significant period of time, i.e., several 100,000 IUs daily for more than 6 months [25, 67, 80]. It is now recognized by many professional medical and nutrition organizations that a 25(OH)D should be at least 30 ng/mL not only for maximum bone health but also to provide the full benefits of vitamin D for overall health and welfare [24, 25, 27, 28, 67].

When considering how much vitamin D we all require it is worthwhile to consider what our hunter-gatherer forefathers were obtaining from daily sun exposure. To get some insight as to what their blood levels likely were, a study in adults was conducted in Maasai herders and Hadzabe bands who lived 2–4° South of the equator in Tanzania and who were outdoors exposed to equatorial sunlight every day. The overall mean concentration of 25(OH)D was 46 ng/mL [81]. Another study determined the amount of daily vitamin D intake required to maintain adequate vitamin D levels in human breast milk to satisfy the infant's requirement. It is well established that human breast milk contains very little if any vitamin D. From an evolutionary perspective this makes little sense. When lactating women received 6000 IUs of vitamin D daily they were able to add enough vitamin D in their milk to satisfy their infant's requirement [82, 83]. This suggests that the hunter-gatherer lactating women exposed to sunlight on a daily basis were making several thousand IUs of vitamin D a day; enough to satisfy their infant's requirement. It is known that once the serum 25(OH)D level reaches 20 ng/mL it takes approximately 100 IUs of vitamin D daily to raise the blood level by approximately 1 ng/mL [25, 67]. When healthy adults in Boston who had a mean 25(OH)D level of 22 ng/mL ingested 1000 IUs of vitamin D daily for 2 months a majority of them were unable to reach a blood level of at least 30 ng/mL [26]. To achieve a blood level of the Maasai and Hadzabe adults of 40–50 ng/mL would require adults to ingest approximately 3000–5000 IUs daily. A study of Canadian adults taking varying doses of vitamin D reported that those who were taking approximately 3000–5000 IUs daily were able to achieve blood levels of 25(OH)D in the range of 40–50 ng/mL. They also reported that adults with a BMI >30, they required 2.5 times more vitamin D to achieve the same blood levels as normal-weight adults. Furthermore, they found that adults taking between 10,000 and 20,000 IUs daily for more than 1 year demonstrated no toxicity [84].

Therefore to achieve a blood level of 25(OH)D of at least 30 ng/mL would require a normal weight adult to ingest at least 1500–2000 IUs daily. To achieve what is considered to be the preferred blood level of 40–60 ng/mL, as recommended by the Endocrine Society, would require ingesting 3000–5000 IUs daily. I recommend to my patients that to guarantee vitamin D sufficiency infants, especially breast-fed infants, should receive at least 400 IUs daily and preferably 1000 IUs daily. Children up to the age of 13 should receive at least 600 IUs daily and preferably 1000 IUs daily. Teenagers should be treated as adults. They should receive at least 1500–2000 IUs daily and up to 5000 IUs daily is reasonable and safe to maintain blood levels of 25(OH)D in the preferred range of 40–60 ng/mL.

The consequences of vitamin D deficiency are often silent, but insidious in nature and have been reviewed extensively [3, 25, 28, 31, 85]. For children, it may prevent them from attaining their peak height and bone mineral density [3, 86]. Adults are at increased risk of developing osteopenia, osteoporosis and increased risk of fracture [25, 28, 86]. In addition, vitamin D deficiency increases the risk of a wide variety of chronic diseases including autoimmune diseases, type 1 diabetes, rheumatoid arthritis, Crohn's disease and multiple sclerosis, cardiovascular disease, neurocognitive dysfunction and Alzheimer's disease, type 2 diabetes, and several deadly cancers [25, 28, 31, 85] (Fig. 2.6).

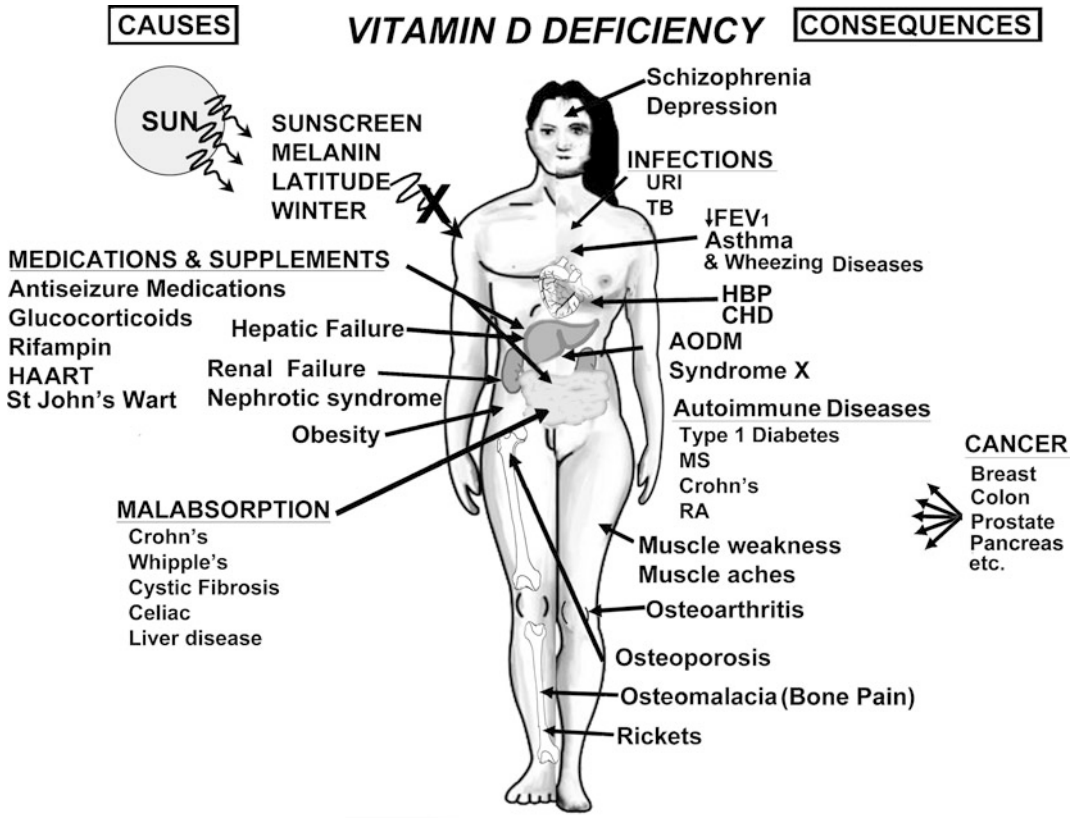

Fig. 2.6 A schematic representation of the major causes for vitamin d deficiency and potential health consequences. (Holick copyright 2007 with permission)

Sunlight, Vitamin D, and the Skin Cancer Conundrum

Humans evolved in sunlight and their skin pigment gene has evolved in order to protect the skin from the damaging effects from excessive exposure to sunlight but permitting enough UVB radiation to enter the skin to produce an adequate amount of vitamin D to sustain health. The pigment gene has rapidly mutated to decrease skin pigmentation [18, 19] in order to permit humans to survive in environments where there is markedly reduced UVB irradiation, and, thus, vitamin D_3 synthesis.

The skin has a large capacity to make vitamin D_3 [24]. When young- and middle-aged adults were exposed one time to one minimal erythemal dose of ultraviolet B radiation, the circulating levels of vitamin D that were observed 24 h after the exposure were similar to adults who ingested between 10,000 and 25,000 IU of vitamin D_2 [87] (Fig. 2.7). Thus, only minimum suberythemal exposure to sunlight is often adequate to satisfy the body's vitamin D requirement [83, 88].

It is well documented that excessive exposure to sunlight will increase the risk of nonmelanoma skin cancers [89]. However, it is also known that occupational sun exposure decreases the risk of the most deadly form of skin cancer, melanoma [90, 91].

People of color who live near the equator and are exposed to sunlight on a daily basis sustain blood levels of 25(OH)D of 40–60 ng/mL [81]. Their skin was designed to produce an adequate amount of vitamin D and the melanin pigmentation prevents the damaging effects minimizing the risk of nonmelanoma skin cancer.

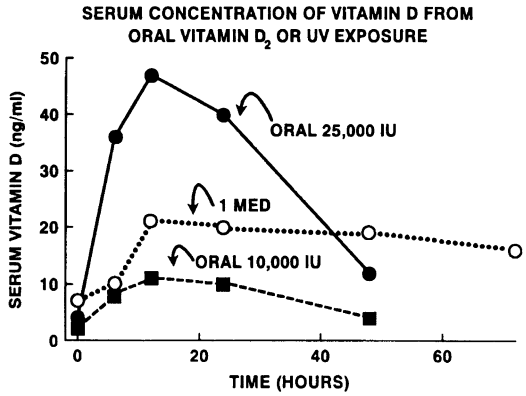

Fig. 2.7 Comparison of serum vitamin D_3 levels after a whole-body (in a bathing suit; trunks for men, bikini for women) exposure to 1 MED (minimal erythemal dose) of simulated sunlight compared with a single oral dose of either 10,000 or 25,000 IU of vitamin D_2. (Holick copyright 2013)

As skin pigment devolved in order to permit humans to produce an adequate amount of vitamin D_3, the skin was perfectly designed to take advantage of the beneficial effect of sun exposure. However, the loss of skin pigment permitted UVB-sensitive macromolecules, including DNA, to absorb the solar UVB radiation that penetrated the epidermis. This absorption caused thymidine dimerization and other alterations in the DNA structure, increasing the risk for the development of nonmelanoma skin cancer [92, 93]. The Surgeon General's report from the United States and many dermatology societies have promoted abstinence from any direct sun exposure, which is thought to be a major contributor for the worldwide vitamin D deficiency epidemic [94].

In support of this recommendation, Peterson et al. [95]. reported that Danish adults exposed to high-intensity sunlight during a vacation in the Marriott Islands had significant and concerning cutaneous DNA damage as measured by increased urinary cyclobutane pyrimidine dimers (CPD), a surrogate for DNA damage. They also reported improvement in vitamin D status and concluded that the detrimental DNA damaging effect of the sun exposure far outweighed the benefits of improvement in the vitamin D status of their subjects. This study however was subject to criticism because Danes with skin types 1 and 2 were not designed to be exposed to high-intensity sunlight for an average of 38 h over 6 days in an environment that was much farther South from where their ancestors evolved. A study by Felton et al. [96] provided a more realistic insight regarding sun exposure and its beneficial and negative health consequences. They exposed healthy adults with little skin pigmentation (skin type II) to low-level simulated United Kingdom June midday sunlight (equivalent to 13–17 min 6 times weekly) and evaluated its effect on vitamin D status and outcome measures related to cutaneous DNA damage. They observed a significant 49% increase in circulating levels of 25(OH)D at the end of the 6-week study. A histologic evaluation of the skin biopsies revealed after the first week of exposure a significant increase in CPD-positive nuclei in keratinocytes compared to the photoprotective skin of the same volunteer. However, remarkably 1 day after the last exposure of the 6-week study, the authors observed significant clearing of the CPD-positive nuclei that corresponded to undetectable levels of CPD in the urine and no change or accumulation in another marker for DNA damage from baseline, i.e., urinary 8-oxo-2′-deoxyguasine (8-oxo-dG), a measure of oxidatively damaged DNA. These results suggested that the skin adapted to the sun exposure and did not demonstrate accumulating DNA damage but did demonstrate that there was likely continued vitamin D_3 synthesis. They also conducted a study in skin type V adults and as expected found minimum histologic evidence for DNA damage and no significant increase in serum 25(OH)D levels. This again demonstrated how the evolution of skin pigmentation evolved for taking advantage of the beneficial effect of sun exposure while minimizing damaging consequences. This suggests that you can have your cake and eat it too when it comes to the utilization of sensible sun exposure to improve a person's vitamin D status [92]. A study in adults who frequent a tanning bed at least once a week at the end of the winter had robust levels of 25(OH)D of approximately 40–50 ng/mL which was comparable to people of color being exposed to sunlight

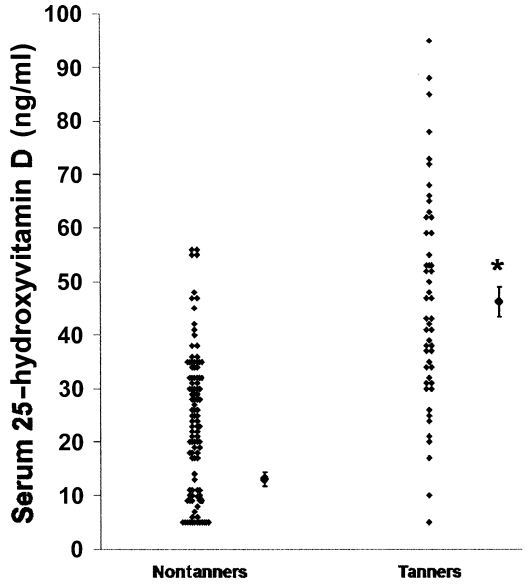

Fig. 2.8 Mean (±SEM) serum 25-hydroxyvitamin D concentrations in tanners and nontanners. Single points for each category are means ±SEMS. ∗Significantly different from nontanners, $P < 0.001$. (Holick copyright 2013)

on almost a daily basis living near the equator [81, 97, 98] (Fig. 2.8).

Aging will dramatically affect the amount of 7-dehydrocholesterol in human skin [99]. As a result, a 70-year-old has about 25% of the capacity to produce vitamin D_3 in their skin compared to a young adult. However, because the skin has such a large capacity to produce vitamin D_3, elders exposed to either sunlight [24, 100], a tanning bed [89, 98] or other UVB emitting devices [100] are able to raise their blood levels of 25(OH)D often above 30 ng/mL.

How long should a person be exposed to sunlight to satisfy their vitamin D requirement? It depends on time of day, season of year, latitude, altitude, weather conditions, and the person's degree of skin pigmentation. Typically for a Caucasian's skin type II living at approximately 42° N in June at noon-time, exposure of arms and legs and abdomen and back when appropriate (and always protecting the face since it is the most sun exposed and sun damaged and only represents about 2–4% of the body surface) to suberythemal sunlight (equivalent to approximately 0.75 MED) on a clear day between the hours of 10 and 3 pm for approximately 10–30 min, two to three times a week is often adequate to satisfy the body's vitamin D requirement. I recently helped develop the free app dminder.info that will provide guidance for sensible sun exposure anywhere on this planet for all skin types. It also provides a recommendation when to stop exposure to direct sunlight and to use sun protection to reduced risk for sun burning. After the sensible sun exposure, the application of a sunscreen with an SPF of at least 30 is then recommended if the person stays outside for a longer period of time in order to prevent sun burning and the damaging effects due to excessive exposure to sunlight.

Conclusion

Humans have always depended on sun for their vitamin D requirement. It is curious that the same UVB radiation that is so beneficial for making vitamin D_3 is also the major cause of non-melanoma skin cancer. It is excessive exposure to sunlight and the number of sunburns that is responsible for the alarming increase in non-melanoma skin cancer [90]. The fact that most melanomas occur on the least sun-exposed areas at least raises the question of whether moderate sun exposure is at all related to an increased risk of this deadly disease. Two reports suggest that moderate sun exposure decreases the risk [90, 91]. It is also worth noting that children and young adults who had moderate sun exposure had a decreased mortality if they developed melanoma [101] and a 40% reduced risk of developing non-Hodgkin's lymphoma [102]. It has also been suggested that improvement in vitamin D status may reduce the risk of developing melanoma and decreasing its malignant activity [103].

It is unfortunate that the sun has been demonized for more than 50 years by those who have been poorly informed or lack knowledge about the beneficial effect of sunlight [104] that our forefathers had appreciated more than 1000 years ago when many cultures including

the Egyptian's worshiped the sun for its life-giving properties [24, 94].

There are several new developments with the important health implications in the photobiology of vitamin D that will need further investigation. Slominski et al. [105] have observed the production of novel vitamin D compounds that have a shortened side chain that have little calcemic activity and potent antiproliferative properties. LED technology has made a major advancement by developing LEDs that can emit ultraviolet C, UVB, and UVA radiation. LEDs can be tuned to emit peak wavelengths with minimum bandwidth. This remarkable advancement in LED technology has resulted in the development of LEDs that emit germicidal UV radiation that is effective for water purification and sterilization of surgical suites and home appliances. We tuned LEDs in the region of the UVB spectrum that maximizes the photoproduction of previtamin D [106]. These LEDs demonstrated that peak wavelengths of 293 and 295 nm radiation were not only very effective in producing previtamin D in human skin but were also approximately 300% more efficient compared to sunlight. This suggests that exposure to LEDs emitting UVB radiation for producing previtamin D improves the risk-benefit ratio by approximately 300%. These LEDs can be developed for naturally producing vitamin D in the skin. This is of particular importance for patients who are unable to absorb vitamin D from diet or supplements because of some type of fat malabsorption syndrome.

Sunscreen technology has been developed whereby the ingredients have been altered in a manner that permits the sunscreen to let an additional small amount of vitamin D producing UVB radiation to pass through it to enhance the production of vitamin D in the skin. This was accomplished without altering its sun protection factor [107].

Finally, it should also be realized that there are a wide variety of additional photochemical and biologic processes that occur in the skin during sun exposure [94, 108]. These include among others an increased production of beta-endorphin, nitric oxide, and carbon monoxide that are related to improvement in feeling of well-being, reduction in blood pressure. In addition, exposure to ultraviolet radiation increased expression of the clock, proopiomelanocortin, aryl hydrocarbon receptor, and nitric oxide synthetase genes [94, 108]. Therefore, sensible sun exposure not only can provide the all-important vitamin D but has demonstrable many other health benefits.

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