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# Sunlight, vitamin D and health: A D-lightful story

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## Abstract

Vitamin D, the sunshine vitamin, has been made on earth for at least 750 million years. Vitamin D evolved during this time into a hormone not only for regulating calcium and bone metabolism, but also for a variety of noncalcemic actions that have been related to decreasing risk of common cancers, autoimmune diseases, infectious diseases and heart disease. Vitamin D requires hydroxylations in the liver and kidneys to be activated to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2$D interacts with its vitamin D receptor in target tissues to enhance intestinal calcium absorption, mobilize calcium from the skeleton and have a wide range of other genomic effects. 1,25$(OH)_2D_3$ is not only made in the kidneys, but made in many other tissues throughout the body for regulating cell proliferation, decreasing cellular malignancy and controlling the production of as many as 200 different gene products. Vitamin D status is determined by measuring serum 25-hydroxyvitamin D [25(OH)D]. A blood level of 25(OH)D > 30 ng/ml is considered to be vitamin D sufficient, whereas < 20 ng/ml is deficient, and 21-29 is insufficient. Sun exposure is a major source of vitamin D for most humans. In the absence of sun exposure, at least 25 μg (1,000 IU) of vitamin $D_3$ is required to satisfy the body's requirement.

## Prehistoric Perspective

Vitamin D, the sunshine vitamin, is recognized for the prevention of rickets in children (1). It was also known that cod liver oil had the same effect as sunlight in the prevention and cure of rickets (1-3). Steenbock and Black (4) noted that Saleeby, who had advocated the greater hygienic utilization of sunlight, suggested that "vitamin D in cod liver oil was probably made by sunlight falling on the green phytoplankton in the far waters of the north Atlantic, and, thence

via other creatures reached the cod". Plankton produce over 120 billion tons of organic carbon per year. A single fish consumes 1.2% of its body weight every 24 hours, and it has been estimated that it takes 0.5 tons of diatoms to make a pound of seal while a pound of killer whale, a predator of seals, requires five tons of diatoms (5,6). Thus, it would not be surprising if phytoplankton were able to produce even small quantities of vitamin D that fish through the concentration of the food chain would be able to obtain a large amount of vitamin D in their diet. It was unknown whether phytoplankton that produced 5, 7-diene sterols (provitamin Ds) were able to convert them to their respective previtamin D derivatives. Holick (5,6) grew 100 liters of *Emeiliani huxleyi*, clone BT-6 (an organism that has existed on earth for at least 750 million years) and *Skeleteonema menzelii* in pure culture to a cell density of about $10^6$ cells per milliliter in glass carboys in the absence of ultraviolet B (UVB); 290-320 nm) radiation. The cells were harvested, resuspended in synthetic sea water and half of the cells were transferred into a quartz vessel and exposed to simulated solar radiation. The high performance liquid chromatography profile of nonirritated cells revealed a presence of provitamin $D_2$ (ergosterol). The cells that were exposed to UVB radiation demonstrated a large peak that was identified as previtamin $D_2$. At room temperature, the previtamin $D_2$ converted to vitamin $D_2$. What was remarkable was that *Emeiliani huxleyi*, which is one of the major phytoplankton species in the Sargasso Sea contained approximately 1.0 microgram of ergosterol per gram wet weight (5).

Although it is not known why phytoplankton make vitamin $D_2$, it has been speculated that the likely reason is that provitamin $D_2$ is incorporated into the lipid bilayer of the plasma membrane sandwiched in between the fatty acid hydrocarbon side chains and polar head groups (7,8). Since provitamin $D_2$ is a rigid planar structure, it fits nicely in between the triglycerides, After exposure to solar UVB radiation, the B ring is opened causing it to form a less rigid previtamin D structure (Fig 1). Once previtamin D converts to vitamin D, it can no longer remain sandwiched in between the triglycerides and is ejected out into the extracellular space.

It has been suggested that the evolution of provitamin $D_2$ may have been for the purpose of acting as a natural sunscreen since provitamin $D_2$, previtamin $D_2$ and vitamin $D_2$ all efficiently absorb solar UVB radiation (5,6). Thus, as early life forms were being bombarded with solar UVB radiation, they needed an efficient method to absorb it without causing covalent linking to important macromolecules including proteins, RNA and DNA. Provitamin $D_2$ and its products would have served as the ideal sunscreen for this purpose (5,6) (Fig 2).

Once vitamin $D_3$ is made and ejected out into the extracellular space, it's possible that it transiently opened up a channel in the plasma membrane permitting the transport of ions such as calcium into the cell. Thus, more than

750 million years ago, the photosynthesis of vitamin $D_2$ may have became intimately linked to cellular calcium homeostasis that has been retained throughout evolution (5,6).

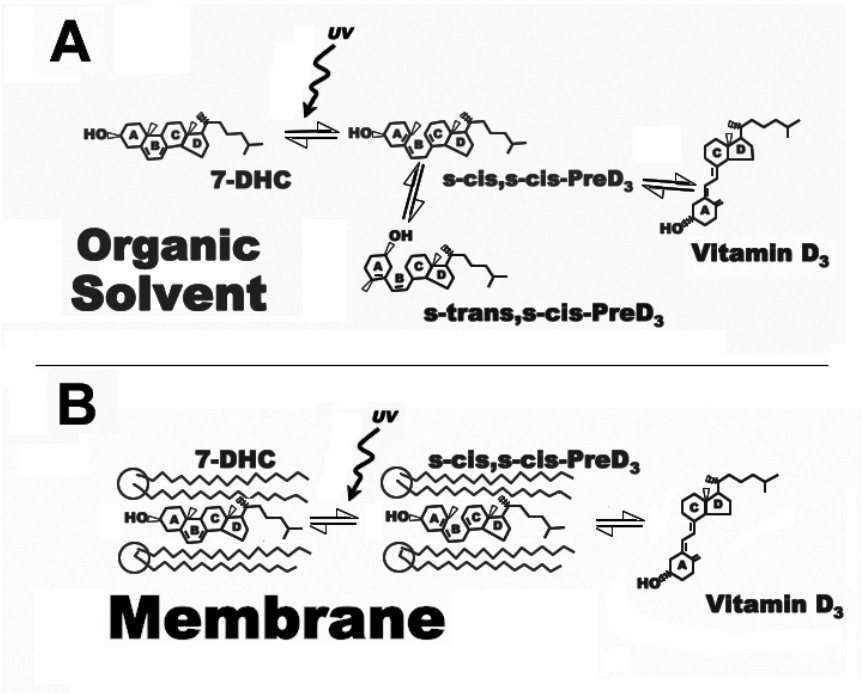


***Figure 1. A:*** *Photolysis of provitamin $D_3$ (pro-$D_3$; 7-dehydrocholesterol) into previtamin $D_3$ (pre- $D_3$) and its thermal isomerization to vitamin $D_3$ in hexane and in skin. In hexane is pro-$D_3$ photolyzed to s-cis,s-cis-pre-$D_3$. Once formed, this energetically unstable conformation 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 $D_3$.*

***B:*** *The s-cis,s-cis conformer of pre-$D_3$ is stabilized in the phospholipid bilayer by hydrophilic interactions between the 3β-hydroxl 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 2007 with permission.*

As life evolved in the ocean, they took advantage of their high calcium environment and used it for controlling neuromuscular function and for many of its metabolic and signal transduction activities. However, once life left the ocean on to terra firma, there was little calcium available because it was locked in the soil. Animals required an efficient method to absorb the calcium that was

present in their diet in order to maintain neuromuscular and skeletal function. It was the exposure to sunlight on the skin producing vitamin D that played a critical role in maintaining calcium homeostasis and promoting the evolution of large vertebrate species including the gigantic dinosaurs.

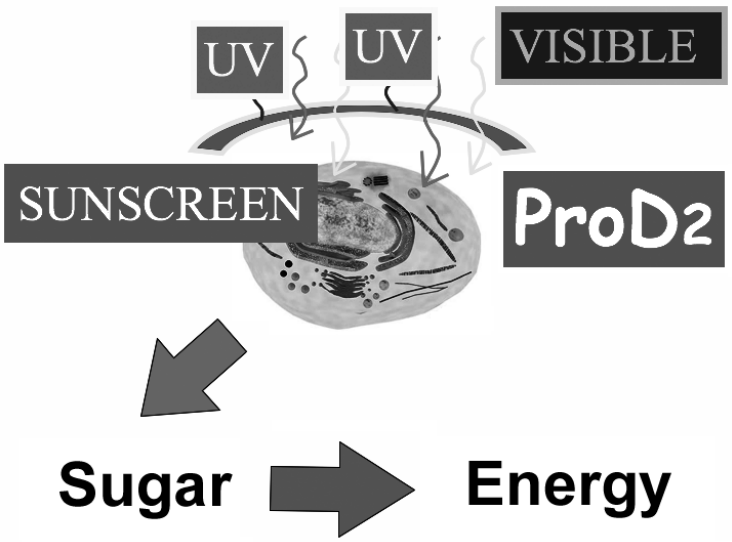


***Figure 2.*** *Schematic suggesting that early in evolution photosynthetic unicellular organisms depended on visible radiation for their energy source. However, the exposure to intense solar ultraviolet B radiation could have quickly caused their demise. Provitamin $D_2$ (ergosterol) in the plasma membrane would have been the ideal sunscreen to efficiently absorb the offending ultraviolet radiation.*

Sixty-five million years ago, the Chicxulub astroid hit the earth and was responsible for the demise of the dinosaurs and the rise of mammals. Although the cataclysmic fires and sunamis played a major role in the extinction process, it is also likely that the large amount of debris deposited into the atmosphere would have resulted in a marked reduction in the penetration of UVB radiation to the point of it being nonexistent. Thus, if dinosaurs depended on sunlight for their vitamin D requirement, this would have been a major catastrophe and could have also been another cause for the extinction. It was the nocturnal mammal that did not require vitamin D to maintain its calcium metabolism that evolved from this catastrophic event (5,6,9).

## Historical Perspective

As humans evolved, they as hunter gathers were always exposed to sunlight, and, therefore, had a plentiful supply of vitamin D. However, with the industrialization of northern Europe in the 16$^{th}$ century, people began

congregating into crowded cities that had buildings several stories tall built in close proximity generating alleyways that prevented any direct sun exposure (1,6). This precipitated a devastating bone disease that was commonly known as rickets. It was Sniadecki (10) who realized that the cause for why his young patients who lived in Warsaw had a high risk of developing rickets was due to the lack of sun exposure since he also observed that his young patients living on farms outside of Warsaw were immune from the disease. Palm (11) in 1889 also appreciated the beneficial effect of sunlight and promoted sunbathing. In 1903, Finsen received a Nobel Prize for the observation that exposure to sunlight was effective in treating a variety of skin diseases including lupus vulgaris caused by mycobacterium tuberculosus infection of the skin (12).

The association of exposure to UVB radiation and the treatment of rickets was first appreciated by Huldschinski et al (13) who showed that rachitic children exposed to a mercury arc lamp had remarkable and rapid healing of their rachitic lesions. Within two years, Hess and Unger (14) reported that exposure to sunlight was equally effective in treating rickets. The appreciation of the antirachitic activity of ultraviolet irradiation of people and animals led to the UV irradiation of food, and ultimately, to the fortification of foods with vitamin D. The fortification of milk with vitamin D helped eradicate rickets as the scourge of the industrial revolution (15).

## Photosynthesis of Vitamin $D_3$

During exposure to sunlight, 7-dehydrocholesterol that is present in the epidermis and dermis absorbs UVB photons with energies of 290-315 nm (16). The absorbed energy causes the double bonds to rearrange causing a break in the bond between carbons 9 and 10 leading to the formation of previtamin $D_3$ (16, 17). (Fig 1, 2) Previtamin $D_3$ exists in two conformeric forms cis,cis and cis, trans. The cis,trans-previtamin $D_3$ is the most stable form, but it cannot convert to vitamin $D_3$. Thus, in an organic solvent, it takes approximately 24 hours for 50% of previtamin $D_3$ to convert to vitamin $D_3$ (9) (Fig 1). From an evolutionary perspective, this takes too long. The previtamin $D_3$ would be destroyed by continued exposure to sunlight. However, since the previtamin $D_3$ is made within the bilayer lipid membrane sandwiched in between the hydrophobic side chains of the triglycerides, the previtamin $D_3$ is conformationally trapped in its thermodynamically unstable cis,cis conformer which rapidly converts to vitamin $D_3$ (9) (Fig 1). Thus, when vitamin $D_3$ is made in either poikliothermic (cold blooded) or warm blooded vertebrates, vitamin $D_3$ is rapidly produced in the skin (9) (Fig 1). Excessive exposure to sunlight will not cause vitamin D intoxication because sunlight degrades any excess previtamin $D_3$ and vitamin $D_3$ (Fig 3).

Once vitamin $D_3$ is made, it is ejected out of the plasma membrane into the extracellular space where it is bound to the vitamin D binding protein (18).

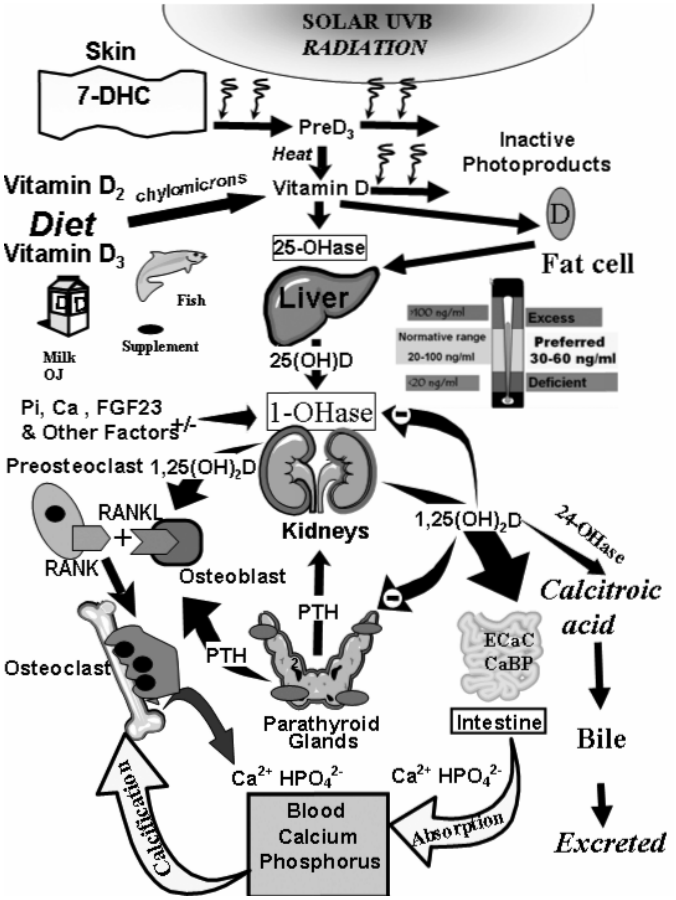


***Figure 3.*** *Schematic representation of the synthesis and metabolism of vitamin D for regulating calcium, phosphorus and bone metabolism. During exposure to sunlight 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin $D_3$ ($preD_3$). $PreD_3$ immediately converts by a heat dependent process to vitamin $D_3$. Excessive exposure to sunlight degrades previtamin $D_3$ and vitamin $D_3$ 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 which transports it to the liver where vitamin D is converted by the vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by 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). 25(OH)D is biologically inactive and must be converted in the kidneys by the 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. Serum phosphorus, calcium, fibroblast growth factor (FGF-23) and other factors can either*

*increase (+) or decrease (-) the renal production of 1,25(OH)$_2$D. 1,25(OH)$_2$D feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. 1,25(OH)$_2$D increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)$_2$D and 25(OH)D to the water soluble biologically inactive calcitroic acid which is excreted in the bile. 1,25(OH)$_2$D enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel (ECaC; also known as transient receptor potential cation channel sub family V member 6; TRPV6)) and the calbindin 9K (calcium binding protein; CaBP). 1,25(OH)$_2$D is recognized by its receptor in osteoblasts causing an increase in the expression of receptor activator of NFκB 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 and maintain neuromuscular function. Holick copyright 2007 with permission.*

## Sources of Vitamin D

The major source of vitamin D for humans is sun exposure. Thus, an increase in skin pigmentation or the topical application of a sunscreen which absorb UVB photons entering into the viable epidermis reduce by as much as 99% the capacity of the skin to produce vitamin $D_3$(1,6,19). Aging markedly reduces 7-dehydrocholesterol levels resulting in a marked reduction in vitamin $D_3$ synthesis (20). An increase in the zenith angle of the sun during winter and early morning and late afternoon results in a longer path length for the UVB photons to travel through the ozone layer which efficiently absorbs them. This is the explanation for why above and below 35° latitude little if any vitamin D is made in the skin during the winter (1,6,21) (Fig 4) This is also the explanation for why in the far northern and southern regions of the world in the summer where the sun shines almost 24 hours a day vitamin $D_3$ synthesis occurs only between the hours of about 10 am and 3 pm (6) (Fig 4).

The major sources of dietary vitamin $D_3$ come from oily fish including salmon, mackerel and herring (22). In the United States, farmed salmon are fed pelleted food that contains little vitamin $D_3$. Thus, it is not surprising that farmed salmon in the United States contain about 10-25% of the vitamin D content compared to wild caught salmon, i.e., approximately 2.5-5.25 mg (100-250 IU) compared to 12.5-25 mg (500-1,000 IU) of vitamin $D_3$/990 gms (3.5 oz) respectively (23). In Europe, farmed salmon are fed fish oil, and, thus, have a vitamin content similar to wild caught salmon. Cod liver oil is an excellent source whereas the flesh of cod and salted cod is not. In the United States, milk and some orange juices,

yogurts and cereals are fortified with vitamin $D_3$. In Europe, margarine is a major source of dietary vitamin $D_3$ (1,22). In the United States, vitamin $D_2$ is sometimes used in food fortification and in some multivitamin supplements.

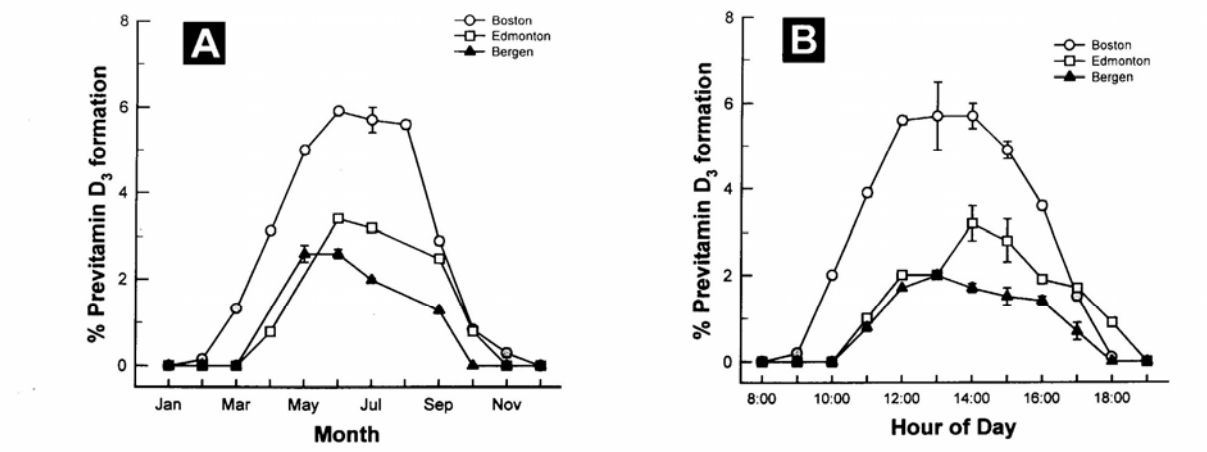


***Figure 4.*** *Influence of season, time of day in July, and latitude on the synthesis of previtamin $D_3$ in Boston (42°N) -○-, Edmonton (52°N) -□-, Bergen (60°) -▲-. The hour is the end of the one hour exposure time in July. Holick copyright 2007 with permission.*

## Vitamin D Deficiency and Its Musculoskeletal Consequences

Once vitamin D (D represents either $D_2$ or $D_3$) is made in the skin or ingested in the diet, it travels to the liver and is converted to 25-hydroxyvitamin D [25(OH)D] (22,24-26). 25(OH)D is converted in the kidneys to its active form 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (Fig 3) . To measure vitamin D status, it is important only to measure 25(OH)D (22). Most experts agree that a 25(OH)D < 20 ng/ml (50 nmol/L) is vitamin D deficiency. Vitamin D insufficiency is defined as a 25(OH)D of 21-29 ng/ml and > 30 ng/ml is considered to be vitamin D sufficiency (22,27).

Vitamin D deficiency is pandemic in children and adults. Studies in the United States, Europe, Middle East, Asia and Australia all have come to the same conclusion, i.e., 30-50% of children and adults are at risk (1,22,27,28). Children and adults of color are especially at high risk due to the inefficient production of vitamin $D_3$. Women who practice purdah and both children and adults who avoid all sun exposure or wear sunscreen protection are equally at high risk(1,22,27,28). Vitamin D deficiency causes a mineralization defect in the skeleton resulting in rickets in children and osteomalacia in adults (1,22,28). It also enhances osteoclastic activity due to secondary hyperparathyroidism which will precipitate and exacerbate both osteopenia, osteoporosis and increase risk of

fracture (22,28-31). The vitamin D receptor (VDR) is present in skeletal muscle (32) and it is well documented that vitamin D deficiency is associated with muscle weakness in both children and adults (22,33). The time to get up from a sitting to standing position and to walk eight feet decreased with increasing serum 25(OH)D levels above 14 ng/ml (33). Nursing home residents receiving 20 μg (800 IU) of vitamin $D_2$/d for five months reduced their risk of falling by 72% (34).

Osteoporosis, which is the loss of the bone mineral and matrix, is not associated with bone pain. However, vitamin D deficiency osteomalacia whereby there is a defect in the mineralization of the collagen matrix results in isolated or generalized achiness in bones, muscles and joints. Patients are often misdiagnosed as fibromyalgia, chronic fatigue syndrome or simply written off as being depressed (22). Of the 150 children and adults (aged 10-65 years) who presented with nonspecific aches and pains in bone and muscles at a Minnesota emergency department and given various diagnoses and sent home on an NSAID or other pain medications, 93% were vitamin D deficient (35). A gentlemen who presented with muscle fasciculations and severe global muscle weakness was diagnosed with amyotrophic lateral sclerosis. He was found, however, to be vitamin D deficient, and correction of his vitamin D deficiency resulted in correction of all of his neuromuscular deficiencies (36).

## Approaches for the Prevention and Treatment of Vitamin D Deficiency

Sensible sun exposure is effective in preventing vitamin D deficiency (1,22). An adult in a bathing suit exposed to 1 minimal erythemal dose (1 MED, slight pinkness to the skin 24 hours after exposure), is equivalent to taking approximately 500 μg (20,000 IU) of vitamin $D_2$ orally (37). Adults who frequented a tanning salon had robust levels of 25(OH)D on average 45 ng/ml and had higher bone mineral density in their hip compared to healthy adults who did not go to a tanning salon in Boston at the end of the winter (38).

In the absence of sun exposure, a minimum of 25 μg (1,000 IU) of vitamin $D_3$/d is needed to satisfy both children and adults' vitamin D requirement (1,22,27,39). Alternatively, giving 1.25 mg (50,000 IU) of vitamin $D_2$ once every two weeks is also effective (22).

To treat vitamin D deficiency, the goal should be to rapidly fill the empty vitamin D tank. Fifty thousand IU of vitamin $D_2$ once a week for eight weeks often is effective assuming that there is no intestinal malabsorption or severe obesity (22,40). Correcting vitamin D deficiency has been demonstrated to be effective in reducing risk of vertebral and nonvertebral fractures

(22,29,30,31,41,42). Three recent studies that did not achieve blood levels of 25(OH)D of > 30 ng/ml demonstrated no antifracture benefit (43-45).

## Nonskeletal Actions of Vitamin D

The VDR is present in essentially all tissues and cells in the body (6,22-26). Furthermore, many tissues including skin, colon, prostate, breast and lung tissue have the ability to make $1,25(OH)_2D$ (2-25,46-50). It is believed that by raising blood levels of 25(OH)D of > 30 ng/ml, that the local production of $1,25(OH)_2D$ may be responsible for many of the health benefits that have been attributed to vitamin D (22,27) (Fig 5, 6). $1,25(OH)_2D_3$ is one of the most potent hormones that inhibits cellular proliferation and induces terminal differentiation (1,22,24,50). There is evidence that $1,25(OH)_2D_3$ is able to unlock genetic information for up to 200 different genes (50,51). It is believed that by raising levels of 25(OH)D > 30 ng/ml that it provides enough substrate to the colon, prostate, breast and other tissues to locally produce $1,25(OH)_2D$. Once formed, $1,25(OH)_2D$ can selectively induce gene transcription for various physiologic processes and also presumably to keep cellular proliferation in check and to prevent cells from becoming malignant (1,22,50,51) (Fig 4).

One practical application for the antiproliferative activity of $1,25(OH)_2D_3$ was to use it for the treatment of the nonmalignant hyperproliferative skin disorder psoriasis (52). Topical application of $1,25(OH)_2D_3$ was shown to be effective in decreasing scaling, plaque thickness and erythema which are the three manifestations of psoriasis (53). Furthermore, it did not cause any significant untoward toxicity. $1,25(OH)_2D_3$ and several of its active analogues including calcipotriene and 1,24-dihydroxyvitamin $D_3$ have been developed commercially for the treatment of psoriasis (52).

$1,25(OH)_2D_3$ and its analogues have been evaluated for treating a variety of cancers. Unfortunately, most studies have either demonstrated little efficacy or no long term efficacy and often was associated with toxicity including hypercalciuria and hypercalcemia (6,25).

It is, however, well documented that living at low latitudes, having more sun exposure throughout life and having higher circulating levels of 25(OH)D have all been associated with a decreased risk of developing and dying of the most common cancers including cancer of the colon, prostate and breast (54-57).

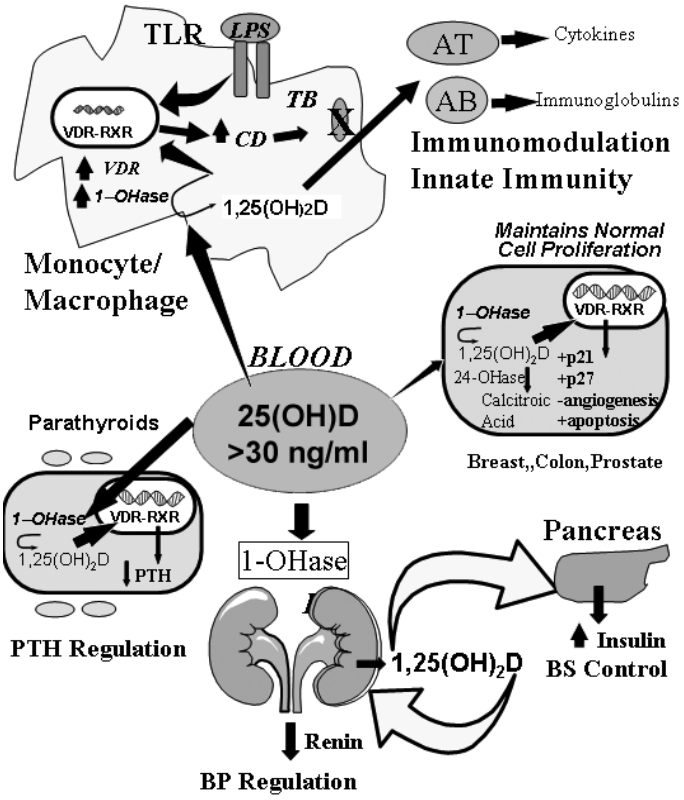


***Figure* 5.** *Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25 dihydroxy-vitamin D 1,25(OH)$_2$D for non-skeletal functions. When a monocyte/ macrophage is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infective agent such as Mycobacterium tuberculosis (TB), or its lipopolysaccharide (LPS) the signal upregulates the expression of vitamin D receptor (VDR) and the 25-hydroxyvitamin D-1-hydroxylase (1-OHase). 25(OH)D levels > 30 ng/ml provides adequate substrate for the 1-OHase to convert it to 1,25(OH)$_2$D. 1,25(OH)$_2$D returns to the nucleus where it increases the expression of 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)$_2$D produced in the monocytes/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, it reduces risk of many common cancers. It is believed that the local production of 1,25(OH)$_2$D 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 induced apoptosis. Once 1,25(OH)$_2$D 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)$_2$D to calcitroic acid which is biologically inert. Thus, the local production of 1,25(OH)$_2$D 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)$_2$D inhibits the expression and synthesis of PTH. The production of 1,25(OH)2D in the kidney enters the circulation and is able to down*

*regulate renin production in the kidney and to stimulate insulin secretion in the β- islet cells of the pancreas. Holick copyright 2007 with permission.*

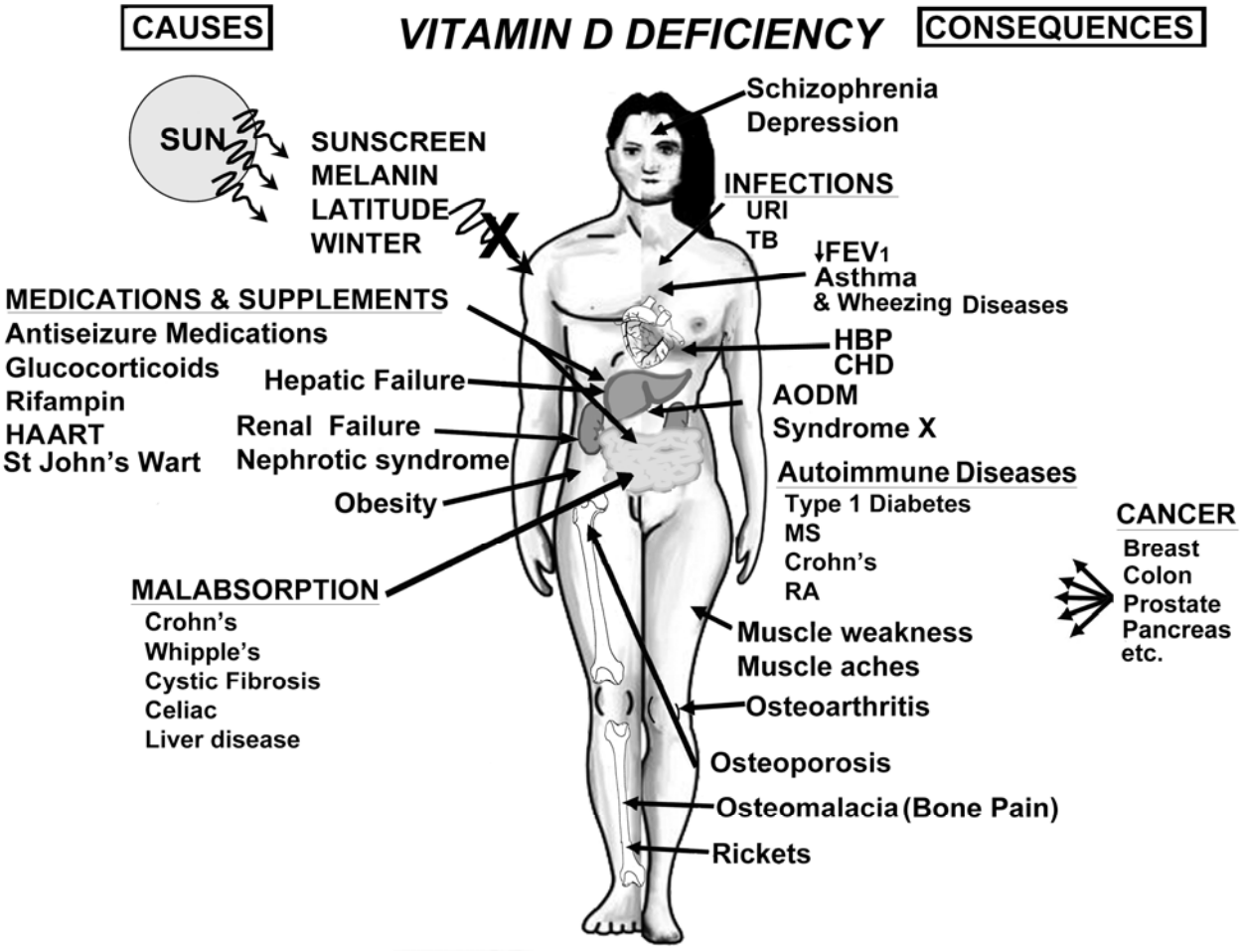


***Figure 6.*** *A Schematic Representation of the Major Causes for Vitamin D Deficiency and Potential Health Consequences. Holick copyright 2007 with permission.*

Other cancers including pancreatic cancer, non-Hodgkins lymphoma, esophageal cancer among others have also been shown to be associated with vitamin D deficiency (58). Lappe et al (59) reported that postmenopausal women who took 27.5 µg (1,100 IU)of vitamin $D_3$/d and 1,000 milligrams of calcium/d for four years reduced their risk of developing cancer by 60%. Thus, at a minimum, a strategy for decreasing a person's risk of cancer should be to raise blood levels of 25(OH)D above 30 ng/ml throughout life (22,27).

Living at higher latitudes and being at higher risk of vitamin D deficiency has also been associated with increase risk of autoimmune diseases including multiple sclerosis and type I diabetes as well as hypertension (1,22,24,60-63). Hypponen et al (64) reported in over 10,000 children who received in the first year of life 50 µg (2,000 IU) of vitamin D/d and followed for 31 years had a reduced risk of developing type I diabetes by 78%. Patients at risk of vitamin D deficiency are at higher risk of developing multiple sclerosis and recent studies suggest that in women and men who had higher serum 25(OH)D levels were less likely by as much as 43% to develop MS (65,66). Rostand (62) reported that living at higher latitudes around the globe was associated with elevated blood pressure. A study of hypertensive adults exposed to a tanning bed that produced vitamin $D_3$ not only raised the blood levels of 25(OH)D by ~ 180%, but also was effective in normalizing the blood pressure (67).

In the 1800's, cod liver oil was used as a way of treating tuberculosis (TB). In the early 1900's, solariums and placing patients at higher altitudes was found to be an effective way of helping to treat TB (12). How sunlight and vitamin D was able to mitigate TB infection was unknown until Liu et al (68) observed that macrophages infected with TB increased gene expression for the VDR and the 25-hydroxyvitamin D-1α-hydroxylase. This resulted in the local production of $1,25(OH)_2D$, which interacted with its VDR, and stimulated the expression of cathelicidin a bacteriocidal peptide that was effective in causing the destruction of TB (Fig 5). Most compelling was their observation that when monocytes were infected with TB in the blood from an African-American with a 25(OH)D of 8 ng/ml that the TB efficiently killed the monocytes. However, when similar monocytes were infected with TB and placed in the same serum but had added to it $25(OH)D_3$ to raise the blood level to 26 ng/ml, they were able to demonstrate an increase in the expression of cathelicidin resulting in the destruction of the TB.

It has also been suggested that influenza outbreaks which occur in the winter time in temperate zones is not due to the cold weather, but rather some other effect that Hope-Simpson suggested was a seasonal stimulus (69). Cannell et al (69) suggested that seasonal stimulus is the nadir in serum 25(OH)D levels. In equatorial countries, influenza is sporadic throughout the year and serum 25(OH)D levels do not fluctuate as much as they do in temperate climates. This intriguing hypothesis has been supported by the observation of Aloia et al (70) who observed that African-American women who ingested 50 µg (2,000 IU) of vitamin $D_3$/d had ~ 90% reduced risk of developing upper respiratory tract infections during the winter months in Long Island, New York.

# Conclusion

Vitamin D deficiency and its insidious health consequences is a worldwide health problem. It is remarkable with the enormity of the evidence-based and research-based information on the role of vitamin D for bone health and for the prevention of many serious chronic diseases has not resulted in any effort by government agencies, the World Health Organization or health professional societies to make as a priority the conquering of vitamin D deficiency and insufficiency. For more than 30 years, the sunscreen industry in collaboration with many dermatology societies have promoted abstinence from direct sun exposure without sun protection. Although it is true that excessive exposure to sunlight and sun burning experiences will increase risk of nonmelanoma skin cancer and wrinkling (71), there is little evidence that sensible sun exposure throughout life which would promote adequate vitamin D stores would significantly increase the risk of either. Melanoma, the most deadly form of skin cancer, has been used as the major reason why abstinence of sun exposure should be practiced. However, it should be appreciated that most melanomas occur on the least sun exposed areas (71,72) and that occupational sun exposure decreases risk of developing melanoma (71-73). Kennedy et al (71) reported that it was bad genetics, the number of moles on a person's body, red hair color, and most importantly, the number of sun burning experiences during childhood that had the greatest association with increased risk malignant melanoma.

The so-called sun safe message promoted in Australia, the "skin cancer capital of the world", has resulted in a marked increase in cases of vitamin D deficiency in both children and adults (74). This has been thoughtfully recognized by the Australian College of Dermatologists and the Cancer Council for Australia and in collaboration with the New Zealand Bone and Mineral Society who have come out with the sensible recommendation that avoidance of excessive sun exposure is warranted to minimize risk of skin cancer, however, moderation in exposure to sunlight should be achieved to promote adequate vitamin D production. Charles Schultz, the famous illustrator of the Peanuts characters got it right in one of his comic strips. Linus sitting on a bench at school opening his lunch receives a note from his mother, and among her other recommendations, suggests, "are you sitting in the sun? I hope so, for a little sun is good as long as we don't over do it perhaps ten minutes a day this time of the year (in San Diego, CA) is about right." He was right on target, and hopefully this message will become universally accepted as a way to promote health.

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