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Vitamin D and Skin Physiology: A D-Lightful Story

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ABSTRACT: Throughout evolution, exposure to sunlight and the photosynthesis of vitamin D_3 in the skin has been critically important for the evolution of land vertebrates. During exposure to sunlight, the solar UVB photons with energies 290–315 nm are absorbed by 7-dehydrocholesterol in the skin and converted to previtamin D_3. Previtamin D_3 undergoes a rapid transformation within the plasma membrane to vitamin D_3. Excessive exposure to sunlight will not result in vitamin D intoxication because both previtamin D_3 and vitamin D_3 are photolyzed to several noncalcemic photoproducts. During the winter at latitudes above ~35°, there is minimal, if any, previtamin D_3 production in the skin. Altitude also has a significant effect on vitamin D_3 production. At 27° N in November, very little (~0.5%) previtamin D_3 synthesis was detected in Agra (169 m) and Katmandu (1400 m). There was an ~2- and 4-fold increase in previtamin D_3 production at ~3400 m and at Everest base camp (5300 m), respectively. Increased skin pigmentation, application of a sunscreen, aging, and clothing have a dramatic effect on previtamin D_3 production in the skin. It is estimated that exposure in a bathing suit to 1 minimal erythemal dose (MED) is equivalent to ingesting between 10,000 and 25,000 IU of vitamin D_2. The importance of sunlight for providing most humans with their vitamin D requirement is well documented by the seasonal variation in circulating levels of 25-hydroxyvitamin D [25(OH)D]. Vitamin D deficiency [i.e., 25(OH)D < 20 ng/ml] is common in both children and adults worldwide. Exposure to lamps that produce UVB radiation is an excellent source for producing vitamin D_3 in the skin and is especially efficacious in patients with fat malabsorption syndromes. The major cause of vitamin D deficiency globally is an underappreciation of sunlight's role in providing humans with their vitamin D_3 requirement. Very few foods naturally contain vitamin D, and those that do have a very variable vitamin D content. Recently it was observed that wild caught salmon had between 75% and 90% more vitamin D_3 compared with farmed salmon. The associations regarding increased risk of common deadly cancers, autoimmune diseases, infectious diseases, and cardiovascular disease with living at higher latitudes and being prone to vitamin D deficiency should alert all health care professionals about the importance of vitamin D for overall health and well being.
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Key words: vitamin D, sunlight, 25-hydroxyvitamin D, altitude, skin

INTRODUCTION

Evolutionary perspective

VITAMIN D IS LIKELY to be one of the oldest if not the oldest hormone that has existed on earth. *Emilianii huxleyi,* a phytoplankton that has survived in the Sargasso sea (Atlantic ocean) unchanged for >750 million years, produced a large amount of ergosterol (provitamin D_2) that was ~0.1% of its dry weight.[1] When this organism was exposed to simulated sunlight, the ergosterol was converted to previtamin D_2, which rapidly converted to vitamin D_2.[1,2] Although it is unknown why these early life forms would produce such a large amount of provitamin D_2, it has been speculated that ergosterol acted as an ideal sunscreen to protect the organism from UVB and UVC radiation, which was most damaging to its UV-absorbing DNA, RNA, and proteins.[1,2]

As life forms left the ocean and ventured onto land, they needed to adapt to the low calcium environment by developing a hormonal system to regulate the efficiency of intestinal calcium absorption. How and why the photosynthesis of vitamin D (D represents D_2 and/or D_3) became responsible for this critically important physiologic function remains unknown. It has been suggested that the association of vitamin D with calcium metabolism may have dated back to early evolution. When ergosterol and/or 7-dehydrocholesterol in the plasma membrane of early life forms was exposed to solar UV radiation, the transformation of the rigid provitamin D structure to a structure with an open B ring would have caused significant change in the membrane structure and fluidity. Furthermore, as previtamin D was transformed into vitamin D, it would be ejected out of the plasma membrane.[2–4] This could have led to an increase in permeability of calcium into the cell. This early membrane

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altering permeability process may have imprinted on all life forms the importance of sun exposure for calcium metabolism both in the oceans and on land. It has been speculated that the demise of dinosaurs and other large vertebrates that occurred 65 million years ago when an asteroid hit the earth was caused by global cooling and loss of most plant life, resulting in starvation. However, another explanation is that these animals would not have been able to make vitamin D, resulting in widespread vitamin D deficiency and its devastating consequences on calcium and bone metabolism. It was the nocturnal rodent that survived the aftermath of the asteroid hit. It is known that the nocturnal rodent had developed a means of needing very little, if any, vitamin D to survive.[5]

Today, amphibians, reptiles, all avian species, and most mammals still depend on sunlight for their vitamin D requirement. Birds are not able to make any vitamin D in skin covered with feathers, and the 7-dehydrocholesterol concentrations are 10-fold higher in nonfeathered skin areas including the legs.[6] For reasons that are not understood, cats have no 7-dehyrocholesterol in their skin and therefore cannot make vitamin D_3 in their skin and depend on their diet for their sole source of vitamin D_3.[7] Skin pigmentation evolved to protect animals and humans from excessive exposure to sunlight, which without it, increased the risk of nonmelanoma skin cancer.[8] However, as hominids migrated north and south of the equator, it is likely that their skin pigment devolved for them to produce enough vitamin D_3 to maintain calcium homeostasis and a healthy skeleton throughout life.[9]

For humans, the lack of sun exposure caused by the industrialization of northern Europe and the United States caused the bone-deforming disease rickets.[10,11] Huldschinski, in 1919,[12] reported the remarkable observation that children with rickets had dramatic healing of their disease after several months of exposure to radiation from a mercury arc lamp. This was quickly followed by Hess and Unger[13] in 1921 reporting that exposure to sunlight was an effective treatment for rickets. This led the United States government to set up an agency that provided guidelines for sensible safe sun exposure for children living in the northeast and who were at risk for rickets.[10,14]

Photobiology of vitamin D

When human skin is exposed to sunlight, the solar UVB photons penetrate into the epidermis and are absorbed by 7-dehydrocholesterol, which is present in the plasma membrane.[2–4] The absorption of these energies transforms 7-dehydrocholesterol into previtamin D_3. Because this photochemical process occurs in the plasma membrane, only the *cis-cis* conformer of previtamin D_3 is formed, which, although thermodynamically unstable, is the only form that isomerizes to vitamin D_3.[3] Once formed, vitamin D_3 is ejected out of the plasma membrane into the extracellular space where it is drawn into the dermal capillary bed by the vitamin D–binding protein.[15]

Anything that influences the number of UVB photons that strikes human skin can have a dramatic impact on the photosynthesis of previtamin D_3. Melanin, which is an effective natural sunscreen and efficiently absorbs UVB photons, markedly diminishes the production of vitamin D_3 in the skin.[16] Similarly, a sunscreen with a sun protection factor of 8 absorbs between 92% and 95% of UVB photons and thus reduces vitamin D_3 synthesis by the same degree.[17] The zenith angle of the sun plays a critical role in vitamin D_3 production. When the zenith angle is more oblique and thus the pathlength through the stratospheric ozone layer is increased, there are fewer UVB photons that are able to reach the earth's surface. It is for this reason that living above ~35° latitude results in little if any production of vitamin D_3 in the skin when the sun's rays are more oblique during the winter months.[3,18] This is also the explanation for why early morning and late afternoon sunlight is very inefficient in producing vitamin D_3 in the skin.[19]

It has been speculated that people living at higher altitudes may be able to more efficiently produce vitamin D_3 in their skin because there is less ozone to absorb the UVB photons. In addition, little is known about the impact that clouds have on the cutaneous production of vitamin D_3.

We evaluated the effect of tanning bed UV irradiation on serum 25(OH)D levels. We used our vitamin D photosynthesis model to determine the efficiency of sunlight for producing previtamin D_3 at various altitudes, times of day, and during cloudy days in the summer and autumn in Boston.

MATERIALS AND METHODS

Evaluation of previtamin D_3 production at various altitudes, times of day, and during cloudy conditions

7-dehydrocholesterol in ethanol was sealed under argon in borosilicate ampoules as previously described.[18] They were placed outside in direct sunlight on cloudless days at 27° N in Nepal and India during the last week of October and during the first 2 wk of November 2006. The lowest altitude was in Agra at 169 m and the highest altitude was at Mount Everest base camp at 5350 m. After exposure for 1 h (from 11:30 a.m. to 12:30 p.m.), the samples were stored in the dark and evaluated by high-performance liquid chromatography (HPLC) for the conversion of 7-dehydrocholesterol to previtamin D_3 and its photoproducts as previously described.[18]

The ampoules were placed outside at 12:00 p.m. for 1 h in June and October on a cloudy day (complete cloud cover, unable to observe the sun, and it was not raining) and on a cloudless day and at 1-h intervals beginning at 6:00 a.m. in Boston.

Influence of season on 25(OH)D levels in nursing home residents

We evaluated circulating concentrations of 25(OH)D by the competitive binding assay as previously described in a group of nursing home residents at various times throughout the year.[20]

Influence of exposure in a tanning bed on circulating concentrations of 25(OH)D

After signing an informed consent approved by the Boston University Medical Center IRB, 15 healthy adults 20–53

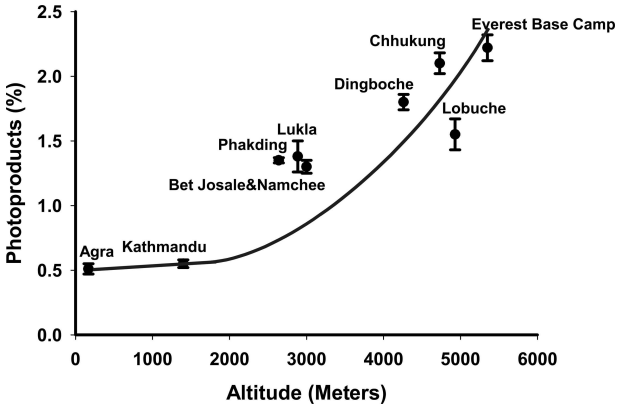

FIG. 1. Ampoules containing 7-dehydrocholesterol in ethanol were exposed for 1 h between 11:30 a.m. and 12:30 p.m. at 27° N in India at various altitudes. The conversion of 7-dehydrocholesterol to previtamin D_3 and its photoproducts was determined by HPLC.

tude of 27° N between the last week of October and the first 2 wk of November 2006 (Fig. 1). In Agra (169 m) and Katmandu (1400 m), ~0.5% conversion of 7-dehydrocholesterol was converted to previtamin D_3 and its photoproducts. There was an almost linear increase in the production of previtamin D_3 and its photoproducts with increasing altitude that was ~400% higher at the base camp of Everest at 5350 m compared with Agra.

Influence of time of day and weather conditions on previtamin D synthesis in Boston

Ampoules containing 7-dehydrocholesterol in ethanol were exposed to sunlight at noon time in June and October. After 5 min in June, ~0.8% of 7-dehydrocholesterol was converted to previtamin D_3, and by 35 min, ~3.3% of 7-dehydrocholesterol was photolyzed to previtamin D_3 and its photoproducts (Fig. 2A). This showed that previtamin D_3 production occurred when 7-dehydrocholesterol was exposed to sunlight and that the efficiency of conversion was almost linear as a function of time over a period of 30 min. Because the zenith angle is much more oblique in the early morning and late afternoon resulting in a longer path length for the solar UV B photons to pass through, we evaluated the effect of time of day on previtamin D_3 synthesis. As can be seen in Fig. 2C, no previtamin D_3 was produced before 8:00 a.m. or after 6:00 p.m. in June in Boston. More importantly, even between the hours of 8:00 and 10:00 a.m. and 4:00 and 6:00 p.m., production was <20% of that produced at midday.

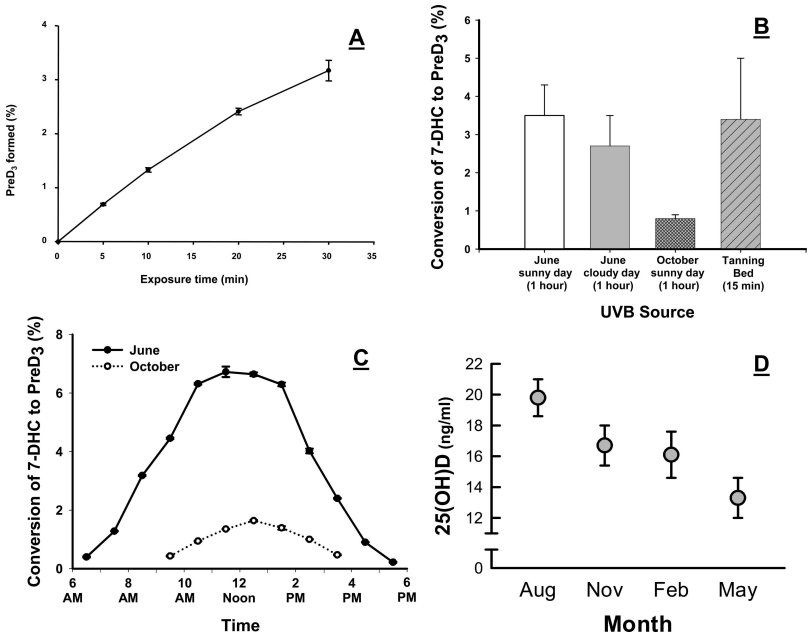

FIG. 2. (A) Ampoules containing 7-dehydrocholesterol in ethanol were exposed to sunlight at noon in June in Boston. HPLC analysis was performed to determine the production of previtamin D_3. (B) An ampoule of 7-dehydrocholesterol (7-DHC) was exposed between the hours of 12:00 p.m. and 1:00 p.m. in June on a sunny day, in June on a cloudy day, and in October on a sunny day in Boston. The conversion of 7-dehydrocholesterol to previtamin D_3 ($preD_3$) was determined by HPLC, and the results were compared with conversion of 7-dehydrocholesterol to previtamin D_3 that occurred in a tanning bed after exposure for 15 min. (C) Conversion of 7-dehydrocholesterol (7-DHC) to previtamin D_3 ($preD_3$) at various times throughout the day in June and in October on a sunny day in Boston. Note that the data points are plotted every half hour to represent what occurred before and 30 min after that time-point (i.e., 6:00 a.m. to 7:00 a.m., etc.). (D) Circulating levels of 25(OH)D were measured in healthy free-living nursing home residents at various seasons of the year.

yr of age received ~0.75 MED (~28 m J/cm^2 for skin type 2 and ~32 mJ/cm^2 for skin type 3) exposure three times a week from a commercial tanning bed that emitted 5% of its UV energy in the UVB range (290–320 nm) to most of their body while in a bathing suit (one piece for men, two piece for women) and wearing eye protection. 25(OH)D levels were determined weekly for a total of 7 wk. The vitamin D synthetic capacity of the tanning bed was determined using the 7-dehydrocholesterol ampoule model system as previously described.[18]

RESULTS

Influence of altitude on previtamin D_3 synthesis

There was a dramatic influence of altitude on the synthesis of previtamin D_3 and its photoproducts at the same lati-

We compared previtamin D_3 production on a cloudless day in June with a cloudless day in October and observed an 80% reduction in the efficiency of conversion of 7-dehydrocholesterol to previtamin D_3 at noon time (Fig. 2B). When we compared the efficiency of conversion of 7-dehy-

drocholesterol to previtamin D_3 on a cloudless day compared with a cloudy day, the efficiency was reduced by ~20%.

We also compared the efficiency of conversion of 7-dehydrocholesterol to previtamin D_3 on a cloudless day in the summer for 1 h compared with radiation from a tanning bed. As can be seen in Fig. 2C, 1 h of sun exposure in June in Boston is equivalent to approximately the same production of previtamin D_3 when exposed to tanning bed radiation for 15 min (~30 mJ/cm^2).

Effect of season and tanning bed irradiation on serum 25(OH)D

Forty-five nursing home residents, as previously described,[21] who were taking a multivitamin that contained 400 IU of vitamin D_2 showed a dramatic decline in their 25(OH)D levels from the end of the summer to the beginning of the following summer. Based on the new definition of vitamin D deficiency [25(OH)D < 20 ng/ml], 49%, 67%, 74%, and 78% of the nursing home residents were vitamin D deficient in August, November, February, and May, respectively, as the mean serum 25(OH)D levels declined (Fig. 2D).

Exposure of 7-dehydrocholesterol to tanning bed irradiation revealed ~1% production of previtamin D_3 after 1 min and a linear increase to ~10% at 10 min (Fig. 3A). Fifteen healthy adults with skin types 2 and 3, 20–53 yr of age, received 0.75 MED whole body exposure three times a week. After 1 wk, there was a 50% increase in 25(OH)D levels that continued to increase over a period of 5 wk to ~150% above baseline levels. The blood levels of 25(OH)D plateaued after 5 wk and were sustained out to 7 wk (Fig. 3B).

A typical increase in 25(OH)D levels is shown in Fig. 3C. This 76-year-old male volunteer was exposed to 0.75 MED in the tanning bed three times a week. His blood level of 25(OH)D increased from 29 to 47 ng/ml after 7 wk. The observed plateau at 2 wk was most likely because of photochemical synthesis and degradation of vitamin D_3,[2,3] because there was no significant increase in the subject's skin pigment throughout the study.

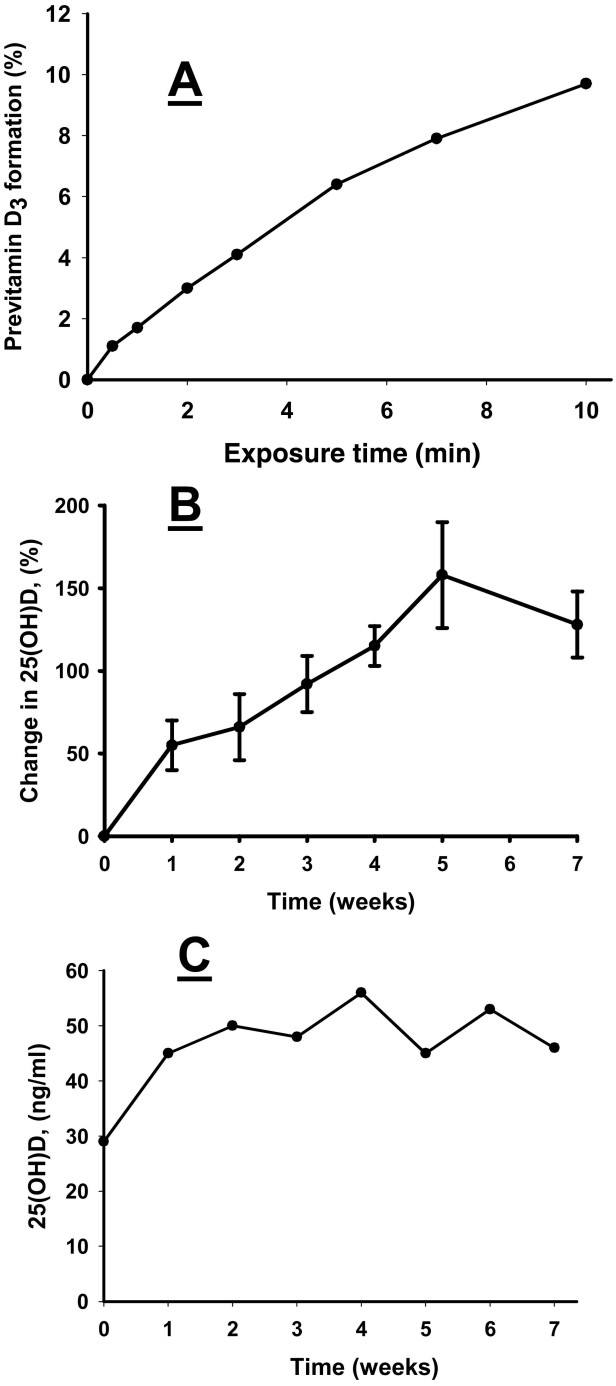

FIG. 3. (A) Ampoules containing 7-dehydrocholesterol were placed in a tanning bed at various times, and conversion of 7-dehydrocholesterol to previtamin D_3 was measured by HPLC. (B) Healthy adults were exposed to 0.75 MED in a tanning bed three times a week for 7 wk. Circulating concentrations of 25(OH)D were determined at baseline and once a week thereafter. (C) A healthy 76-year-old man was exposed to tanning bed radiation equivalent to 0.75 MED three times a week for 7 wk. His circulating concentrations of 25(OH)D were obtained at weekly intervals.

DISCUSSION

As early as 1941,[22] it was observed that living at higher latitudes in the United States increased risk of dying of cancer. Since that initial observation, it has now been observed that living at higher latitudes and being more prone to vitamin D deficiency markedly increases risk of many deadly cancers including cancer of the colon, prostate, breast, esophagus, etc.[23,24] Living at higher latitudes also increases risk of having hypertension,[25] type I diabetes,[26] multiple sclerosis[27] and other autoimmune diseases,[28] and infectious diseases including tuberculosis and influenza.[15,16]

There is compelling new literature that suggest that the recommendations made in 1997 for adequate vitamin D[29] intakes in the absence of sunlight are totally inadequate.[30–33] Most experts now agree that a minimum of 1000 IU of vitamin D_3 a day is necessary to maintain circulating concentrations 25(OH)D of ≥30 ng/ml.[33,34]

Humans have depended on sunlight for their vitamin D requirement. The impact of season, time of day, and latitude on vitamin D synthesis is well documented.[2,3] We now report that altitude also has a dramatic influence on vitamin D_3 production and that living at altitudes above ~3500 m permits previtamin D_3 production at a time when very little is produced at latitudes below 3400 m. It was surprising that, at 27° N in Agra (169 M), little previtamin D_3 production was observed. However, there was significant air pollution that caused a haze over the city. It is likely the ozone and other UVB-absorbing pollutants in the air prevented the solar UVB photons from reaching the earth's surface to produce previtamin D_3.

Artificial light sources are an excellent method for producing vitamin D_3 in the skin. This has been especially effective for patients with fat malabsorption syndromes who are unable to absorb any oral intake of vitamin D_3 from either dietary or supplemental sources.[35] We and others have reported that exposure to UV radiation increases circulating concentrations of 25(OH)D.[36–38] We report that exposure to tanning bed radiation for an equivalent of 0.75 MED three times a week is very effective in raising blood levels of 25(OH)D and supports the observation that adults who frequent a tanning bed at least once a week in the winter time maintain robust levels of 25(OH)D of >45 ng/ml.[39]

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