Ultraviolet B Radiation: The Vitamin D Connection

12

Michael F. Holick

Abstract

Vitamin D is known as the sunshine vitamin. During exposure to sunlight the skin transforms 7-dehydrocholesterol into vitamin D_3. Throughout evolution vitamin D_3 has played a pivotal role in the evolution of vertebrates. Vitamin D is not only critically important for bone health but has a multitude of other biologic functions to help reduce chronic illnesses. This Chapter reviews how vitamin D is produced in the skin, factors that affect its production and a prospective on how to obtain vitamin D from sensible sun exposure.

Keywords

Sunlight • Vitamin D • Rickets • UVB radiation • Vitamin D deficiency

12.1 Prehistoric and Historic Perspectives

As life evolved in the ocean it took advantage of the sun's energy to generate a variety of photochemical compounds essential for the evolution of life on earth. Photosynthesis resulted in the generation of carbohydrates to provide energy source for these early life forms. In addition to the production of carbohydrates during exposure to visible radiation early life forms were also producing vitamin D as a result of being exposed to solar ultraviolet radiation. One of the early phytoplankton species, Emiliania huxlei (a coccolithophore which has calcium carbonate containing exoskeleton) which has existed unchanged in the Sargasso Sea (the Atlantic Ocean) for more than 250 million years was found to have a large quantity of the vitamin D_2 precursor ergosterol. When exposed to ultraviolet radiation that it was converted ultimately to vitamin D_2 [1]. Thus the photosynthesis of vitamin D has been occurring throughout evolution in organisms exposed to sunlight. Although the function of ergosterol and vitamin D2 are unknown in these primitive organisms it has been suggested that one of the functions was to act as a natural sunscreen to efficiently absorb

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ultraviolet B (UVB; 290–320 nm) radiation that was potentially damaging to UV sensitive macromolecules including DNA. Recently it was observed that vitamin D was most effective in prolonging the lifespan of the round worm Caenorhabditis elegans by improving protein homeostasis and slowing the aging process [2].

It was also speculated that early vertebrates including the dinosaurs required vitamin D to maintain a healthy skeletal structure. Their quick demise could've been caused in part by their inability to produce any vitamin D as a result of the asteroid strikingly earth and releasing into the atmosphere from its impact and fires so much debris that it prevented any vitamin D producing radiation from reaching the earth surface. Curiously nocturnal rodents adapted to their sunless environment and did not require vitamin D to survive. Ultimately it was these nocturnal rodents that gave rise to the evolution of hominids and humans [1].

Most vertebrates exposed to sunlight are able to produce vitamin D in their skin with the exception of cats that apparently obtained their vitamin D from their dietary sources. Captive vertebrates including amphibians, reptiles and nonhuman primates are at extremely high risk for vitamin D deficiency and metabolic bone disease due to lack of direct sun exposure [3, 4]. The vitamin D producing ultraviolet radiation is absorbed by glass and thus these animals require dietary vitamin D or exposure to artificial ultraviolet radiation to maintain a healthy skeleton and normal calcium metabolism [5].

For humans the lack of sun exposure as a result of the industrial revolution resulted in a devastating bone disease commonly known as rickets [6, 7]. This disease was recognized in the mid 1600s that caused severe growth retardation and skeletal deformities especially of the lower legs. The first insight for the role of sunlight for bone health was made by Sniadecki in 1822 when he reported that from his experience as a physician he observed that rickets was common in children living in Warsaw Poland and he very seldom observed rickets in children living in the rural areas outside of this industrialized city. He made the association that it was lack of sunlight in the dark and poorly lit streets in Warsaw that was responsible for this devastating skeletal disorder [6–8]. 70 years later Palm reported that from his clinical experience in London and contacts with his colleagues who were in India and China that rickets was extremely common in London and yet his colleagues reported back to him that rickets was uncommon in children living in squalor in India and China. He concluded the only common denominator that could explain this dramatic difference was the fact that the pall of smoke from coal burning in the atmosphere and buildings built in close proximity prevented any sunlight from reaching children who were outside in London. He advocated sunbathing to treat and prevent rickets [7, 9].

It was incomprehensible to the medical community at the time to believe that exposure of the skin to sunlight could have any beneficial effect of the skeleton and the observations by Sniadecki and Palm [7] were dismissed. It wasn't until 1919 when Huldschinsky reported that exposure of children to radiation from a mercury arc lamp was effective in improving mineralization of the skeleton based on the analysis of x-rays before and after the exposure for several weeks. He also reported that exposure of one arm to the ultraviolet radiation was effective in improving the mineralization of the bones in the unexposed arm as it did in the exposed arm. He concluded that as a result of the ultraviolet radiation exposure something was produced in the skin that circulated in the body to have an effect on the skeleton in the arm not exposed to the mercury arc lamp [7, 10, 11].

Two years later Hess and Unger exposed children with rickets to sunlight on the roof of their hospital in New York City and reported significant improvement in their rickets [12]. Thus it was established that exposure to ultraviolet radiation and sunlight were effective in treating and preventing rickets.

However it was also perplexing that rickets in dogs and children could be treated effectively with cod liver oil. Originally it was considered that the vitamin A in cod liver oil had antirachitic activity. However when cod liver oil was heated and exposed to oxygen which destroyed vitamin A activity the antirachitic activity remained

intact. This resulted in McCollum calling this new antirachitic factor vitamin D [7, 10, 13, 14].

By the turn of the twentieth century more than 90% of children living in the Netherlands and North Eastern United States had evidence of rickets [7]. A large campaign was mounted worldwide to find the cause and cure for this crippling metabolic bone disease [13]. A study in rodents demonstrated that cod liver oil was as effective as exposure to UV radiation in treating rickets [7]. Thus it was concluded that the antirachitic factor in cod liver oil could be produced in the skin when exposed to sunlight. As a result of these observations Steenbock and Black [15] and Hess and Weinstock [16] began exposing a variety of foods including cotton seed oil, corn oil and milk to ultraviolet radiation demonstrated this process produced the antirachitic factor and was effective in preventing rickets in rodents.

It was also recognized at the same time that yeast exposed to UV radiation resulted in the production of the antirachitic factor. An analysis of the yeast resulted in the identification of the precursor of vitamin D as ergosterol. As a result ergosterol was added to milk as well as wide variety of other foods and drinks followed by exposure to ultraviolet radiation resulting in them having antirachitic activity [6, 7, 17]. It was initially the irradiation of milk containing ergosterol that was effective in preventing rickets in children. Once it was determined that the ergosterol was the precursor of vitamin D it was irradiated and the irradiated product was added to milk to fortify it with the antirachitic factor, vitamin D. This process quickly eliminated rickets as a significant health problem in countries that fortified their milk with vitamin D [6, 7].

At the same time in the early 1930s departments of Health in the United States and UK also advocated sensible sun exposure for the prevention of rickets [7, 10, 13]. Originally it was assumed that the vitamin D produced in human skin during sun exposure was the same as the vitamin D produced in UV irradiated yeast. However it was observed that the vitamin D produced from irradiated yeast was less effective in its antirachitic activity in chickens when compared to vitamin D obtained from the irradiation of pig skin [7, 13, 17]. It was finally demonstrated by Windaus that the precursor of vitamin D in mammalian skin was from the precursor of cholesterol, 7-dehydrocholesterol not ergosterol. The difference between the 2 provitamin D's was a double-blind between C22 and C23 and a methyl group on C24 [7, 13, 17].

12.2 The Photochemistry and Photobiology of Vitamin D

In the 1940s a major effort was undertaken to understand the photochemistry of vitamin D. It was demonstrated that during exposure to UV radiation 7-dehydrocholesterol underwent a ring opening between carbons 9 and 10 to form previtamin D_3. It was found that previtamin D_3 was thermodynamically unstable and rearranged its three double bonds (triene) to form the thermodynamically stable vitamin D_3. It was also observed that continued exposure of previtamin D_3 to UV radiation produced a variety of photoproducts including lumisterol, tachysterol and toxisterols [7, 18].

In the 1980s studies were conducted to understand the photochemistry of vitamin D in human skin (Fig. 12.1) [19–21]. An evaluation of the action spectrum for vitamin D_3 (efficiency of various wavelengths in producing vitamin D_3) in human skin revealed that the wavelengths most effective for producing previtamin D_3 were around 298 nm and that UVA (wavelengths above 315 nm) was ineffective (Fig. 12.2) [7, 19]. It was also observed that during prolonged exposure to UVB radiation (290–315 nm) that previtamin D_3 photo isomerized to lumisterol and tachysterol [21]. This observation revealed that sun exposure regulates the production of previtamin D_3 and that excess exposure does not result in the production of intoxicating amounts of vitamin D_3 [20]. Originally it was thought that melanin pigmentation not only in decreased risk for developing skin cancer but also prevented excessive vitamin D from being produced in the skin [22]. Although the former is true the latter is not since sunlight itself is responsible for regu-

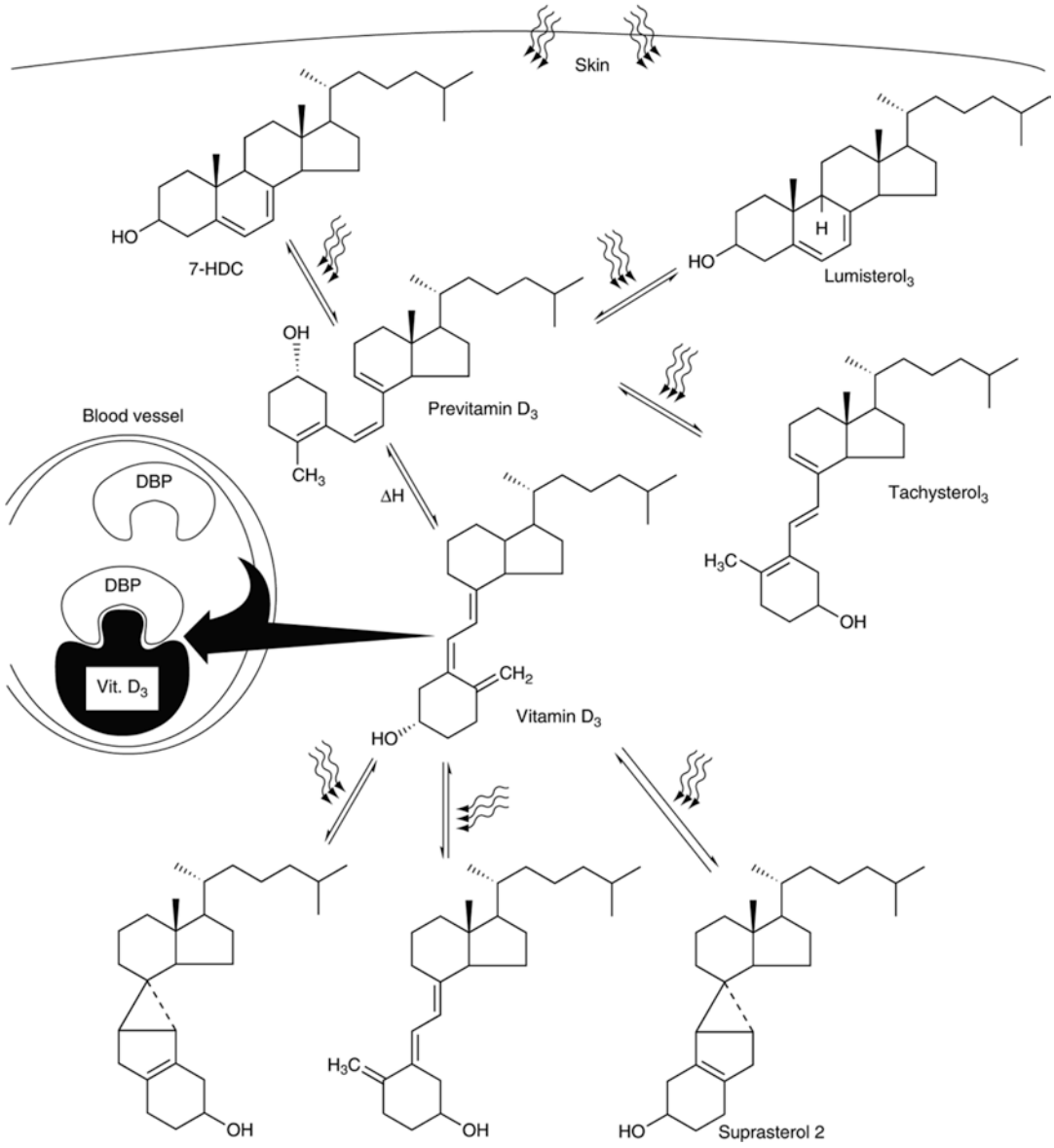

Fig. 12.1 A schematic representation of the photochemical and thermal events that result in the synthesis of vitamin D_3 in the skin, and the photodegradation of previtamin D_3 and vitamin D_3 to biologically inert photoproducts. 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D_3 by the action of solar ultraviolet B radiation. Once formed, previtamin D_3 is transformed into vitamin D_3 by a heat-dependent (ΔH) process. Vitamin D_3 exits the skin into the dermal capillary blood system and is bound to a specific vitamin D-binding protein (DBP). When previtamin D_3 and vitamin D_3 are exposed to solar ultraviolet B radiation, they are converted to a variety of photoproducts that have little or no activity on calcium metabolism (Holick, copyright 1995 with permission)

lating the production of vitamin D_3 in the skin. No more than 15% of 7-dehydrocholesterol is converted to previtamin D_3. The continued exposure to sunlight results in the production of lumisterol and tachysterol setting up a photoequilibrium (Fig. 12.3). Prolonged exposure to UVB radiation will also converted to previtamin D_3 and its photoproducts to other photoproducts known as toxisterols (Fig. 12.4) [7]. These were originally thought to have toxic properties which

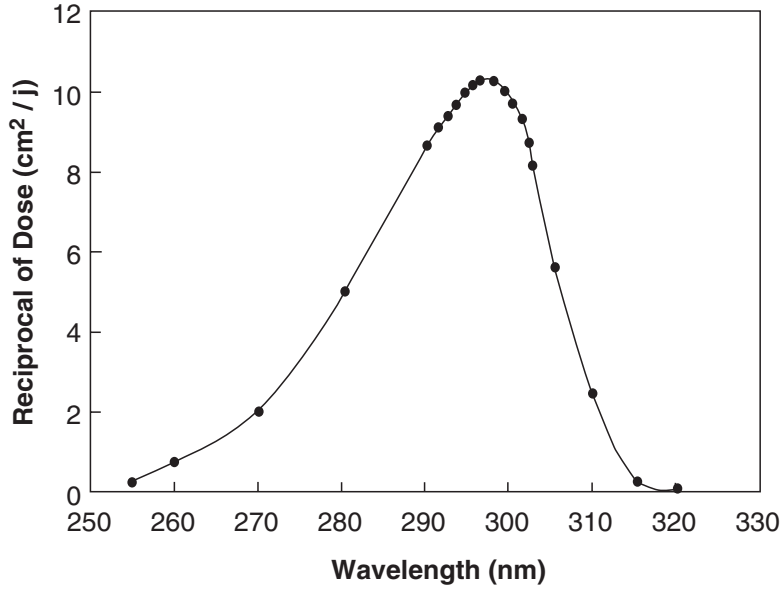

Fig. 12.2 Action spectrum for the conversion of 7-dehydrocholesterol to previtamin D_3 in human skin (Holick, copyright 2007. Reproduced with permission)

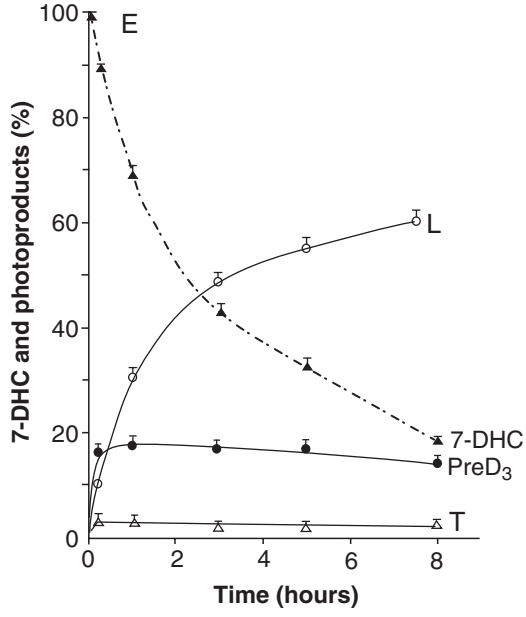

Fig. 12.3 An analysis of the photolysis of 7-dehydrocholesterol (7-DHC) in the basal-cell layer and the appearance of the photoproducts previtamin D_3 (Pre-D_3), lumisterol$_3$ (L), and tachysterol$_3$ (T) with increasing time of exposure to equatorial simulated solar ultra violet radiation. *Bars* above data points show the standard error of the mean of three determinations (Holick, copyright 1981. Reproduced with permission)

is why they were called toxisterols. Vitamin D_3 also will photo isomerized when exposed to ultraviolet B radiation forming suprasterols and 5, 6-trans-vitamin D_3 [7].

The conversion of previtamin D_3 to vitamin D_3 is a temperature-dependent process. At room temperature it takes several days for this process to be completed. Even at body temperature it takes more than a day for most of the previtamin D_3 to be converted to vitamin D_3. However when reptile skin and human skin was exposed to ultraviolet B radiation it was observed that the conversion of previtamin D_3 to vitamin D_3 was approximately tenfold more rapid compared to previtamin D3 isomerizing to vitamin D_3 at the same temperature in an organic solvent [23]. It was quickly determined that this was not due to an enzymatic reaction but rather due to a novel nonenzymatic membrane mediated catalytic mechanism. The 7-dehydrocholesterol being a planar molecule is sandwiched in between the fatty acid hydrocarbon side chain with the 3-hydroxyl oriented to the polar head group of triglyceride in the plasma membrane. When 7-dehydrocholesterol absorbs UVB radiation it undergoes a bond cleavage between carbons 9–10 to form the thermodynamically unstable cis-cis conformer which is maintained within the triglyceride permitting it to rapidly convert to vitamin D_3 and not to its more

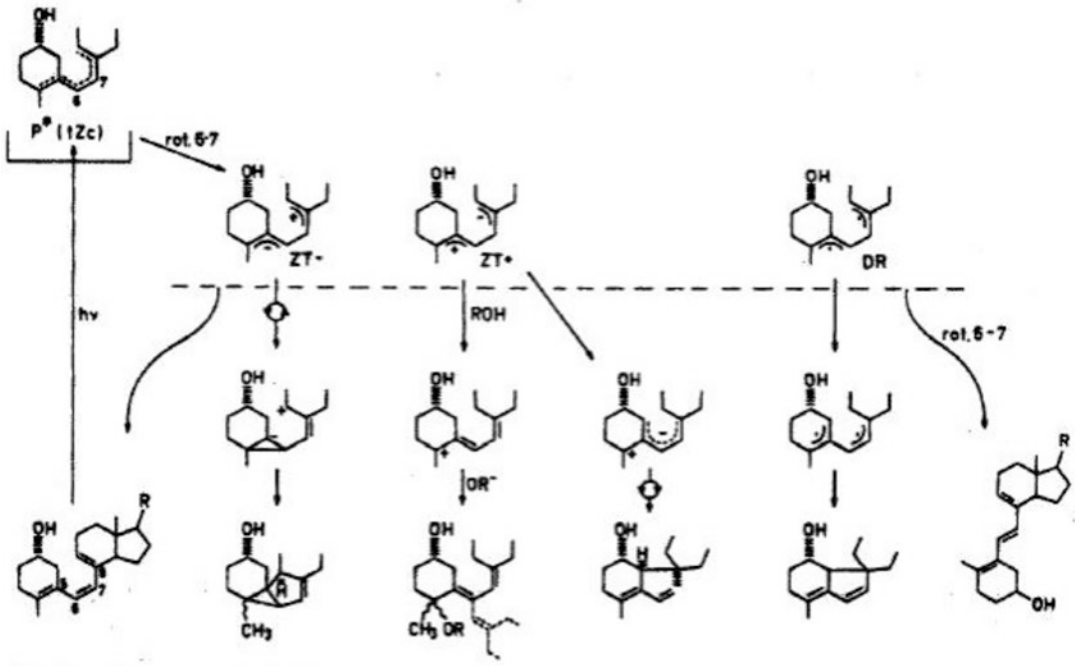

Fig. 12.4 Once previtamin D_3 is formed, it has the ability to rotate around the 6-7 bond. Relaxation via rotation about the 6-7 bond followed by UV irradiation can give rise to a wide variety of toxisterols and tachysterol

thermodynamically stable cis-trans conformer which is not able to isomerize to vitamin D_3 as demonstrated in Fig. 12.5 [7].

12.3 Factors Affecting the Cutaneous Production of Previtamin D3

It had been assumed that one of the driving forces in evolution for dark skinned pigmentation was for the prevention of excessive amounts of vitamin D from being produced that could potentially cause toxicity [22]. However is now recognized that sunlight itself regulates the cutaneous production of vitamin D_3 [7, 20, 24]. Thus melanin pigmentation did not evolve to prevent vitamin D intoxication. However melanin is extremely efficient in absorbing UVB radiation and therefore competes with 7-dehydrocholesterol for solar UVB radiation reducing its conversion to previtamin D_3 [25]. A person with skin type 5 and 6 (never burns always tans) therefore requires a much longer exposure time usually about 5–10 times more compared to a person with skin type 2 (always burns and sometimes tans). This is the explanation for why people of color are at much higher risk for vitamin D deficiency.

Sunscreens mimic melanin and efficiently absorb UVB radiation. A sunscreen with a sun protection factor of 30 applied properly would be expected to absorb approximately 97–98% of the UVB radiation striking the skin and therefore reduces the skin's capacity to produce vitamin D_3 by 97–98% [26].

As stratospheric ozone efficiently absorbs solar UVC (180–290 nm) and a large amount but not all UVB radiation (290–315 nm) is the explanation for why approximately only 1% of the solar UVB radiation ever reaches the earth surface. An increase in the path length by which UVB radiation passes through results in a further decrease in how much UVB radiation reaches the earth surface (Fig. 12.6). This phenomenon explains why time of day, season, latitude, altitude as well as weather conditions have such a dramatic effect on the cutaneous production of vitamin D_3 [7, 27]. The zenith angle of the sun is

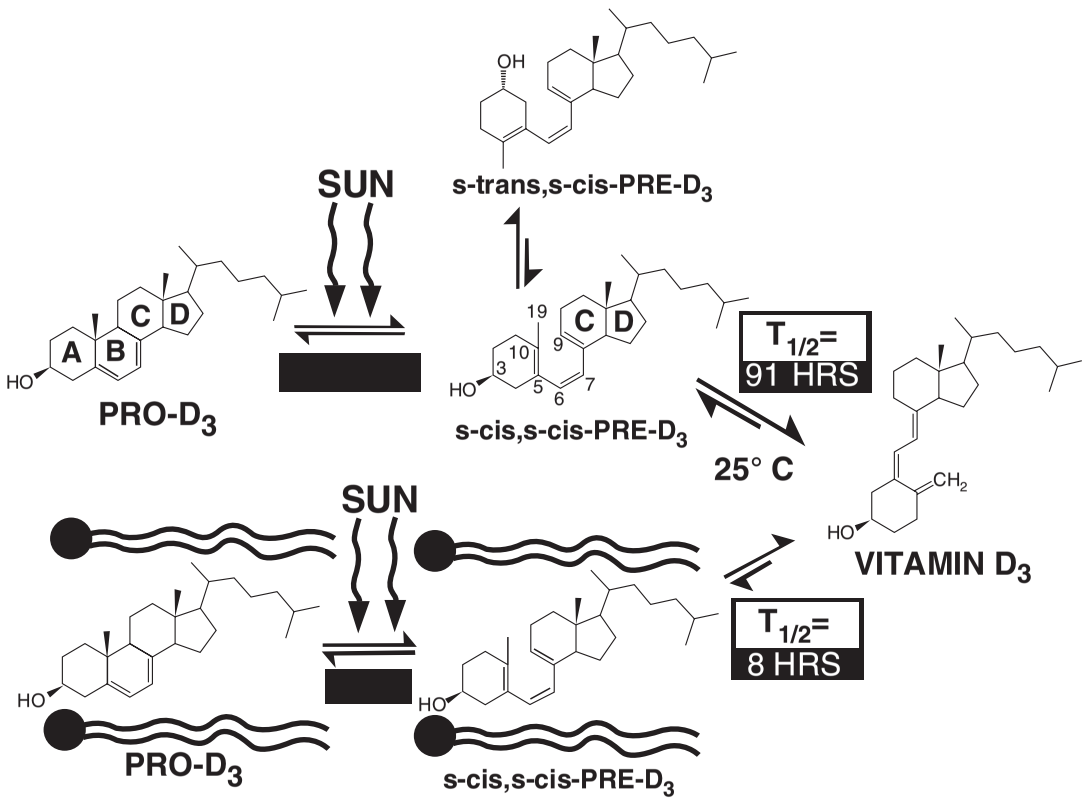

Fig. 12.5 Photolysis of provitamin D_3 (pro-D_3. 7-dehydrocholesterol) into previtamin D_3 (pre-D_3) and its thermal isomerization to vitamin D_3 in hexane and in lizard skin at 25 °C. In hexane pro-D_3 is photolyzed to s-cis,s-cis-pre-D_3. Once formed, this energetically unstable conformation undergoes 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 3ß-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 1995. Reproduced with permission)

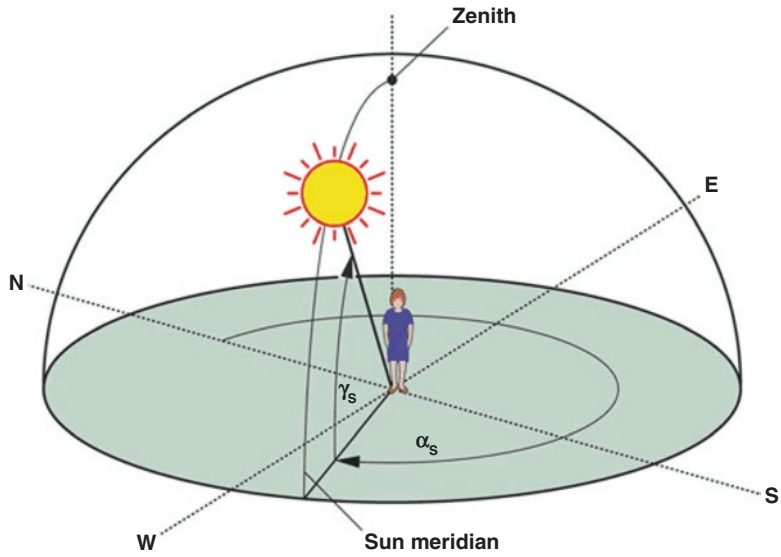

Fig. 12.6 The solar zenith angle is the angle made by the sun's light with respect to the vertical (the sun being directly overhead). This angle is increased at higher latitudes, early morning and late afternoon when the sun is not directly overhead, and during the winter months. As the solar zenith angle increases, the amount of UVB radiation reaching the earth's surface is reduced. Therefore, at higher latitudes, greater distance from the equator, more of the UVB radiation is absorbed by the ozone layer thereby reducing or eliminating the cutaneous production of vitamin D_3 (Holick, copyright 2006. Reproduced with permission)

more oblique in the early morning and late afternoon explaining why very little vitamin D is produced before 9 AM and after 3 PM even in the summertime. The higher latitude for more oblique is the angle of the sun explaining why very little if any vitamin D is produced in the skin during the winter months. In Boston 42° North very little if any vitamin D is produced between November and March. 10° further North in Canada or Europe very little if any vitamin D is produced between October and April (Fig. 12.7) [27]. Clouds as well as air pollution absorb UVB radiation reducing the efficiency of the sun in producing vitamin D3 in the skin. The higher the altitude shorter is the path length and therefore the cutaneous production of vitamin D3 is much more efficient. In Agra, India (169 m) in November at 27° North latitude very little previtamin D3 was produced during sun exposure. An evaluation of previtamin D3 production traveling to base camp of Mt. Everest revealed a gradual increase in the production of previtamin D3 with increasing latitude reaching a maximum of about 400% higher at 5350 m compared to Agra [28].

12.4 The Role of Sunlight and Other Sources of UVB Radiation in Contributing to Vitamin D Status

Once vitamin D_3 is produced in the skin or ingested in the diet and travels to the liver where it is converted to 25-hydroxyvitamin D [25(OH)D] [29, 30]. This is the major circulating form of vitamin D used by doctors to measure a person's vitamin D status. Studies have shown that blood levels of 25(OH)D very with season with a peak blood level occurring at the end of the summer and then nadir at the end of the winter. Hours of sunshine in Denmark was directly associated with blood levels of 25(OH)D [31] (Fig. 12.8). A study of 3.8 million blood samples collected over a two-year period of time in the United States revealed that there was a definite seasonal variation in the circulating blood levels of 25(OH)D [32]. There was also a significant latitudinal effect with blood samples collected in the southern United States having higher circulating

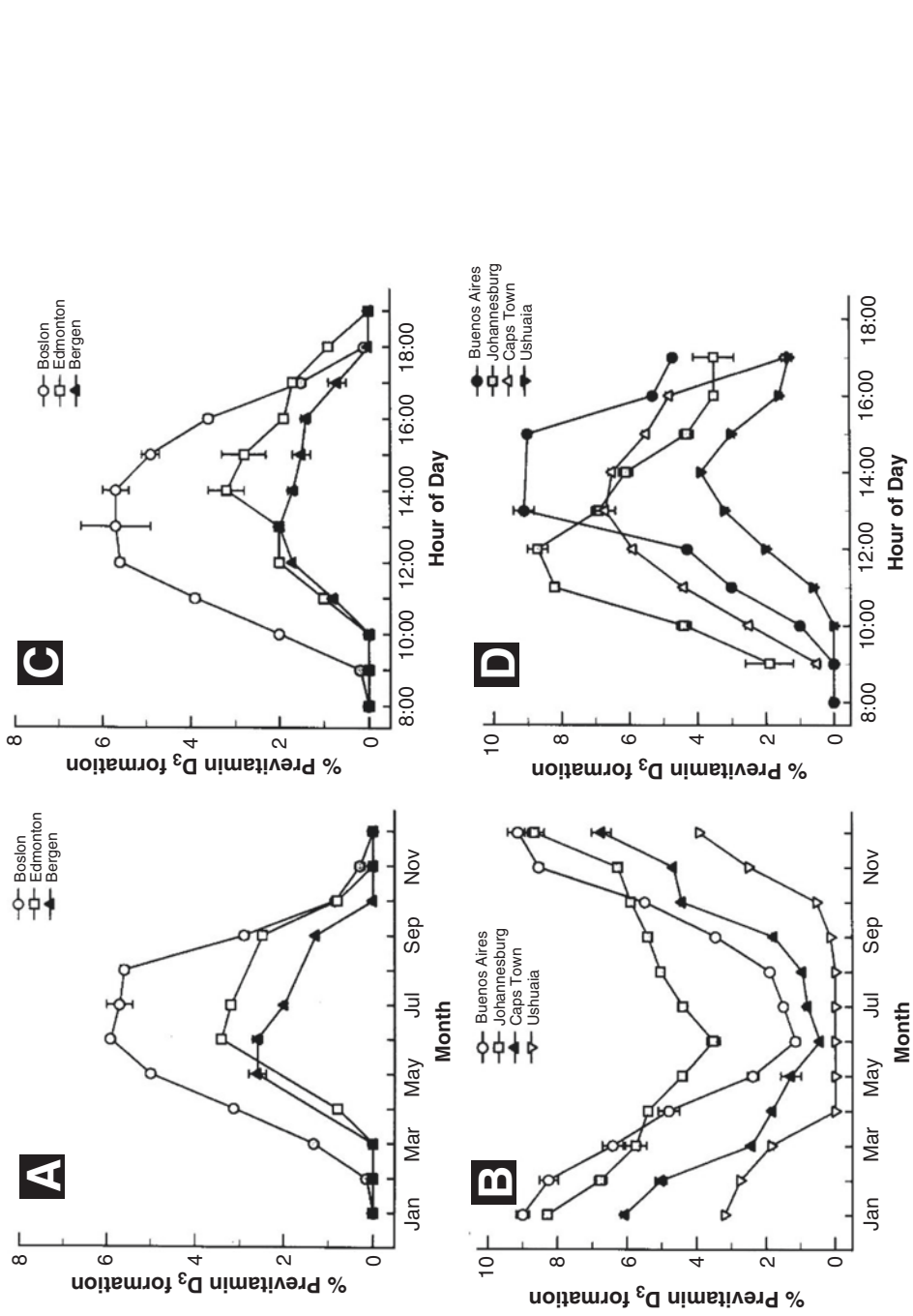

Fig. 12.7 Influence of season, time of day, and latitude on the synthesis of previtamin D_3 in Northern (A and C) and southern hemispheres (B and D). The hour indicated in C and D is the end of the 1-h exposure time (Holick, copyright 1998. Reproduced with permission)

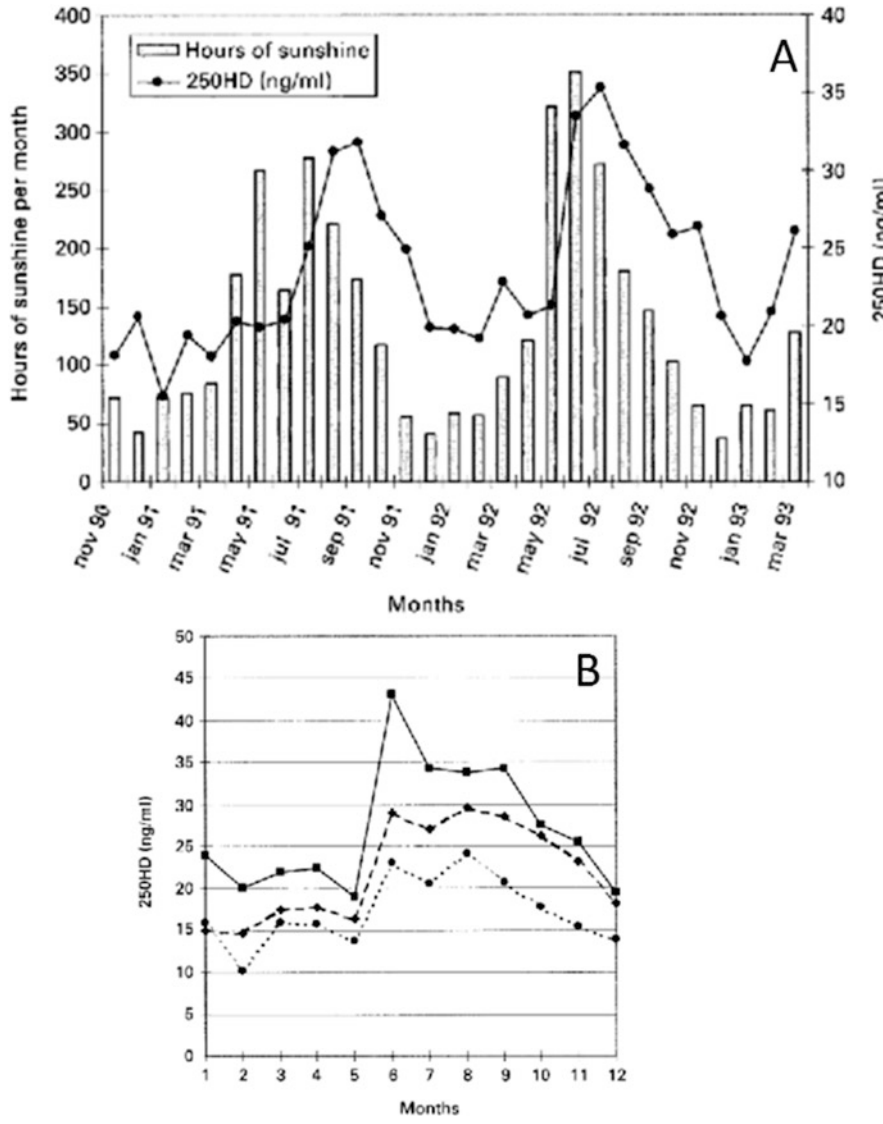

Fig. 12.8 (**a**) Seasonal fluctuation of serum 25(OH)D in healthy perimenopausal Danish women and relationship between hours of sunshine and serum 25(OH)D. (**b**) Seasonal fluctuation of serum 25(OH)D according to frequency of sun exposure. ■, regular sun exposure; ◆, occasional sun exposure; ●, avoiding direct sun exposure (Holick, copyright 2013. Reproduced with permission)

25(OH)D levels at the end of the winter (24 ng/mL) compared to samples collected at the same time from adults living in Northern United States. The study also demonstrated that the contribution of season was very significant. The mean blood levels of 25(OH)D at the end of the winter in northern United States was 21 ng/mL and at the end of the summer rose to 29 ng/mL. This seasonal variation had also a significant physiologic effect on the blood levels of parathyroid hormone (PTH). There was an inverted relationship between PTH and blood levels of 25(OH)D with a 4 week lag time. Thus at the end of the summer PTH levels reached their nadir 4 weeks later and at the end of the winter when 25(OH)D reached its nadir PTH levels were at their highest level 4 weeks later (Fig. 12.9).

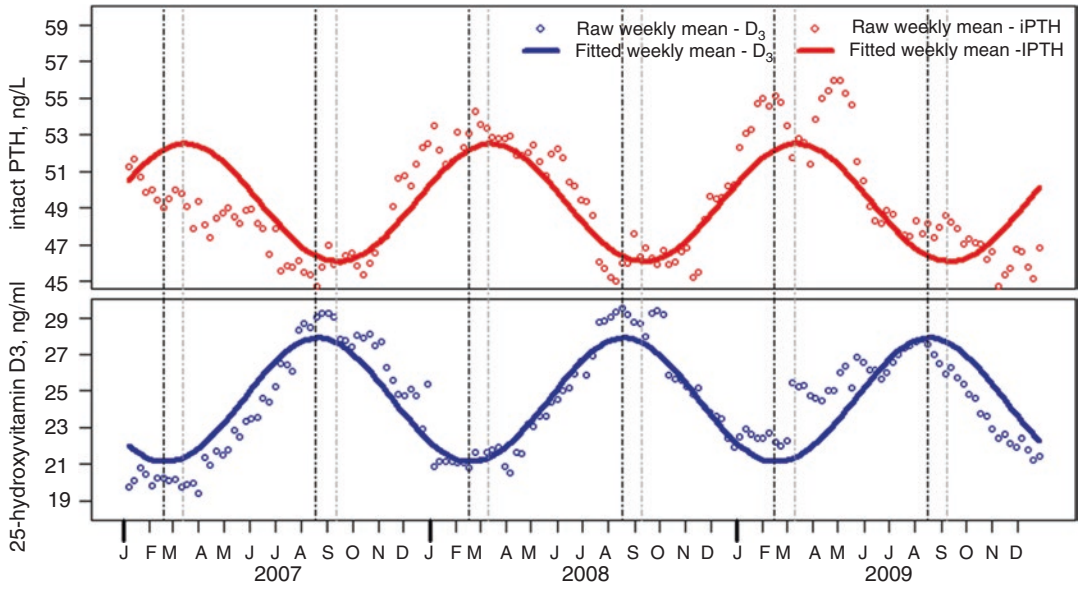

Fig. 12.9 Seasonal Variation of 25-Hydroxyvitamin D3 (bottom panel) and Intact PTH (iPTH) (*top panel*) Weekly Mean Values. The maximum seasonal variation of 25(OH) D3 (peak to trough) was 6.8 ng/mL, reaching its trough in the 8th week (early March) of each year and its peak in the 34th week (early September). Peak iPTH values occurred at week 12 (early April) and trough values at week 37 (late September), a pattern that is roughly reciprocal to that of 25(OH)D3, but lags by 3.5 weeks. Individual points represent the mean of the normalized distribution for each week. The *solid* lines represent the fit. *Dark vertical dashed* lines represent 25-hydroxyvitamin D3 peaks and troughs, and *light vertical dashed* lines represent the iPTH peaks and troughs. To convert 25-hydroxyvitamin D3 from ng/mL to nmol/L, multiply by 2.496 (rounded as 2.5) (Holick, copyright 2015. Reproduced with permission)

Human skin has a large capacity to produce vitamin D. When healthy adults in a bathing suit had their whole bodies exposed to one minimal erythemal dose (slight pinkness to the skin 24 h after the exposure; MED) of UVB radiation in a tanning bed they raised their blood levels of vitamin D to ~20 ng/mL which is equivalent to ingesting approximately 20,000 IUs of vitamin D (Fig. 12.10) [7]. Studies in surgically obtained humans skin have also demonstrated that approximately 250 ng (10 IUs)/in2 of vitamin D is produced when exposed to one MED of UVB radiation [33]. A study in healthy adults who used a tanning bed at least once a week were found to have mean blood levels of 25(OH)D of 48 ng/mL. Healthy adults matched for sex and age at the same time had a mean blood level of 25(OH)D of 18 ng/mL [34].

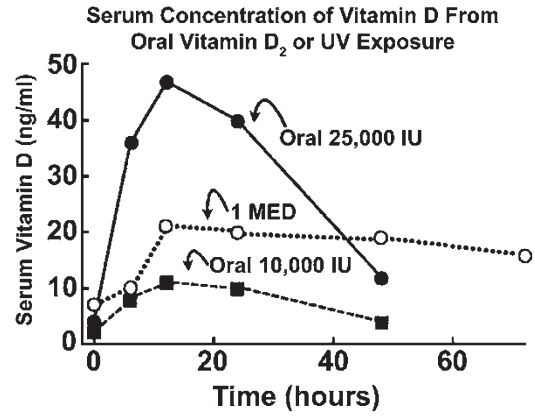

Fig. 12.10 Comparison of serum vitamin D_3 levels after a whole-body exposure (in a bathing suit; bikini for women) to 1 MED (minimal erythemal dose) of simulated sunlight compared with a single oral dose of either 10,000 or 25,000 IU of vitamin D_2 (Holick, copyright 2004. Reproduced with permission)

12.5 Ultraviolet B Induced Extrarenal Synthesis of 1,25-Dihydroxyvitamin D

Once vitamin D is made in the skin or ingested in the diet it travels to the liver to be converted to 25(OH)D. Once formed it reenters the circulation and travels to the kidneys where it is converted to its active form 1,25-dihydroxyvitamin D [1,25(OH)2D] [29, 30]. Patients with chronic kidney disease who are unable to produce $1,25(OH)_2D$ results in a decrease in the efficiency of intestinal calcium absorption leading to a transient decrease in the blood calcium levels. This is immediately recognized by the parathyroid glands resulting in an increase in the production of parathyroid hormone. This causes secondary hyperparathyroidism which results in a metabolic bone disease of the skeleton known as renal osteodystrophy. $1,25(OH)_2D_3$ (calcitriol) and its active analogs have been effectively use for the prevention and treatment of secondary hyperparathyroidism and renal osteodystrophy [29]. However these medications can cause hypercalcemia limiting their use in some patients.

It is recognized that variety of cells and organs not responsible for calcium metabolism also have the capacity to convert 25(OH)D to 1,25(OH)2D including activated monocytes and macrophages and keratinocytes [29, 30]. It had in previously reported that patients with chronic kidney disease who while on dialysis and have no kidney function often have measurable levels of $1,25(OH)_2D$. Is thought that uremia associated with chronic kidney disease that activate monocytes which have the capacity to produce $1,25(OH)_2D$ [35, 36].

It had been previously reported that keratinocytes have a large capacity to convert 25(OH)D to $1,25(OH)_2D$ [37]. It has also been reported that keratinocytes express not only the 25(OH)D- 1 alpha hydroxylase but also the vitamin D-25 -hydroxylase [38]. In vitro studies reported that vitamin D3 added to culture the skin cells could be converted to 1,25(OH)2D3 [39].

This was the rationale conducting a study in patients with chronic kidney disease on hemodialysis to expose them to UVB radiation to determine if this would be effective not only in raising blood levels of vitamin D_3 but also increase the blood levels of $25(OH)D_3$ and $1,25(OH)_2D_3$. 95 chronic kidney disease patients (mean a 62 years) on hemodialysis were treated with a mean dose of 35,000 IUs of vitamin D_3 a week while a group of 14 patients (mean age 51 years) received whole body UVB radiation for 6 months. Skin biopsies were obtained in 3 patients. The group receiving oral vitamin D_3 raised their blood levels of $25(OH)D_3$ by 60% over 18 months compared to an increase of 400% in the group that received UVB radiation for 6 months. In a group of 4 patients who received suberythemal exposures to UVB radiation for up to 10 years also were able to maintain normal circulating levels of $1,25(OH)_2D_3$ (Fig. 12.11). The skin biopsies confirmed that the epidermal cells were expressing the VDR as well as the vitamin D-25-hydroxylase and the 25(OH)D-1- alpha hydroxylase [38].

The 14 patients who received the UVB irradiation for 6 months show an increase in their hematocrit and required less erythropoietin. They demonstrated an increase in maximum oxygen uptake and work load capacity that was associated with decreased lactic acid production. They also demonstrated decreased heart rate and

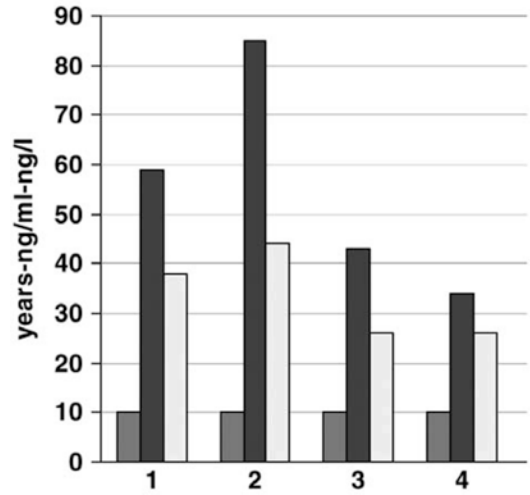

Fig. 12.11 *Vitamin D status of 4 hemodialysis patients over 10 years received suberythemal UVB irradiation one to three times weekly (Vit D_3: gray bars; $25(OH)D_3$: black bars; $1,25(OH)_2D_3$: white bars)* (Holick, copyright 2016. Reproduced with permission)

systolic and diastolic blood pressure with an increase in the R-R interval and beat-to-beat differences [40].

12.6 Sunlight, Skin Cancer and Vitamin D

Sunlight has been and continues to be a major source of vitamin D for children and adults worldwide [7, 41]. The introduction of sunscreens and the worldwide publicity campaign recommending avoidance of all direct sun exposure because of concern for increased risk for skin cancer, has cause a vitamin D deficiency pandemic [42]. Globally 30–40% and 60–80% of children and adults have been reported to be vitamin D deficient based on The Institute of Medicine's definition for maximum bone health and vitamin D insufficiency based on the endocrine Society's definition for maximum bone and muscle health respectively [30, 43–47] (Figs. 12.12 and 12.13).

Most skin cancer is due to excessive exposure to sunlight and the number of sun burning experiences especially as a child and young adult. These cancers, known as melanoma and non-melanoma skin cancer, typically appear the most sun exposed and sun damaged areas including the face, top of the ears and top of the hands [48, 49]. A study in Danish adults who were exposed to high intensity sunlight for 38 h over a 6 days during a vacation in the Canary Islands were able to improve their circulating levels of 25(OH)

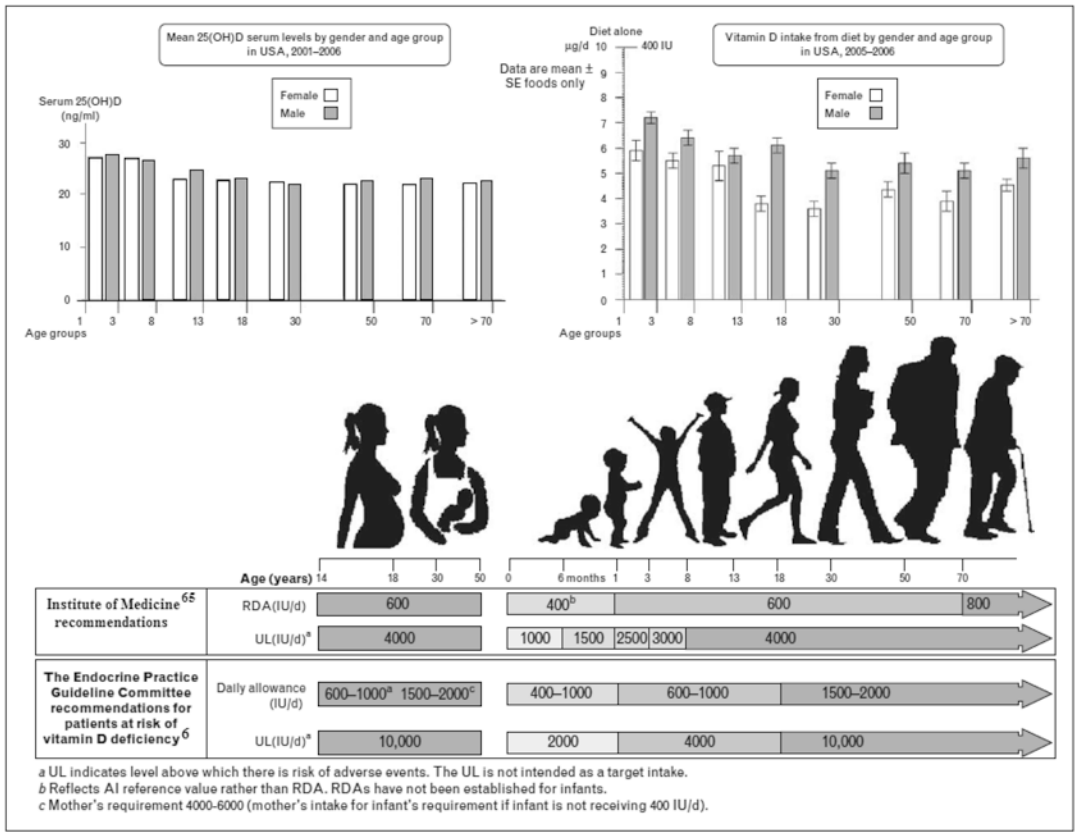

Fig. 12.12 Vitamin D intakes recommended by the Institute of Medicine and the Endocrine Practice Guidelines Committee. 25(OH)D[25-hydroxyvitamin D]; AI [adequate intake]; RDA [recommended dietary allowance]; SE [standard error]; UL [tolerable upper intake level] (Copyright Holick 2013, reproduced with permission)

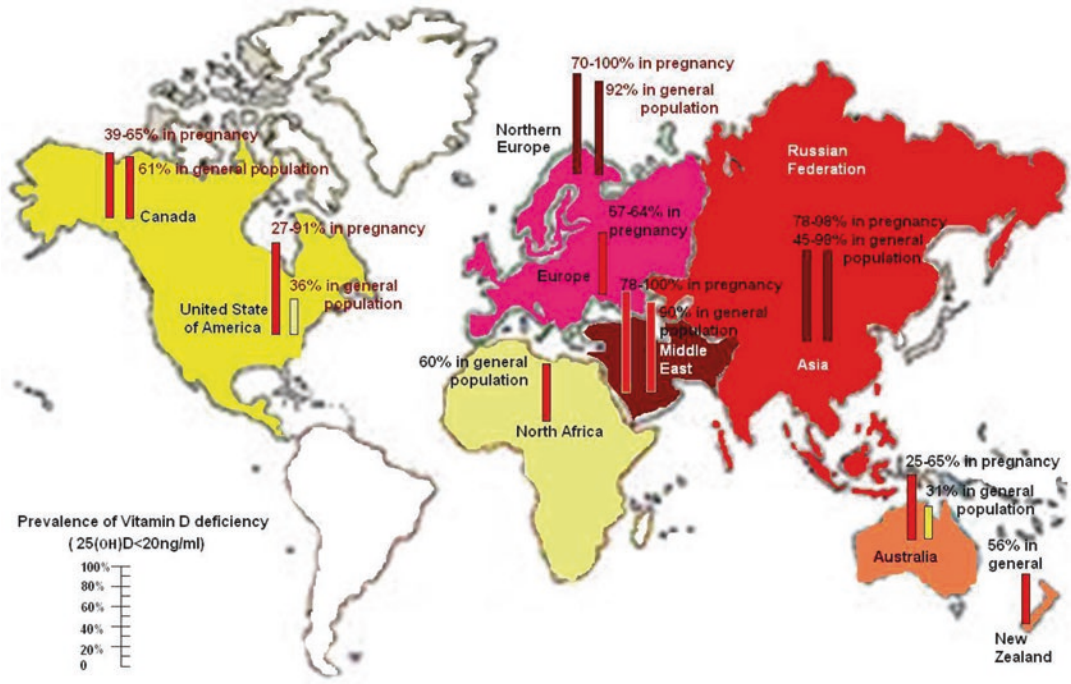

Fig. 12.13 Reported incidence of vitamin D deficiency defined as a 25-hydroxyvitamin D (25[OH]D) level below 20 ng/mL around the globe in pregnant women and the general population. To convert 25(OH)D values to nmol/L, multiply by 2.496 (Copyright Holick 2013, reproduced with permission)

D. However. Peterson et al. [50] also observed a significant and concerning cutaneous DNA damage as measured by increased urinary cyclobutane pyrimidine dimers (CPD), a surrogate for DNA damage. Thus, it was suggested that you could not have your cake and eat it to, i.e. take advantage of the beneficial effect of sun exposure for producing the vital vitamin D_3 without significant DNA damage in the skin. From an evolution perspective this makes little sense since sun-induced synthesis of vitamin D_3 was essential not only for the evolution of none human vertebrates on terra firma but was also essential for the maintenance of skeletal health for hominids including present-day humans [51]. Felton et al. [52]expose healthy British adults with skin type 2 and 4 to an amount of simulated sunlight typical for what would occur during the summer in the UK. Those with skin type 2 received simulated June midday sun light for approximately 13–17 min 6 times weekly for 6 weeks. They reported a 49% increase in circulating levels of 25(OH)D. Initially they observed that this exposure resulted in the formation of CPD and other pyrimidine photoproducts that if unrepaired have been associated with increased risk for nonmelanoma skin cancer. However 24 h after the last exposure skin biopsies and urine revealed significant clearing of the CPD-positive nuclei. This 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′-deoxyguanosine (8-oxo-dG), a measure of oxidatively damaged DNA. They compared skin type 2 with type 5, and found that there was more DNA damage done to those with type 2, supporting that our ancestors who migrated further from the equator were at a disadvantage when it comes to UVB skin protection. As has been previously reported, increased skin protecting pigmentation efficiently absorbs UVB radiation and therefore also reduces the number of photons absorbed by 7-dehydrocholesterol, resulting in a decrease in

the effectiveness of the sun in producing vitamin D_3,which they also observed by demonstrating a statistically insignificant increase in serum 25(OH)D levels in their Asian subjects. These data support the concept that skin pigment began to devolved as a result of the migration of humans north and south of the equator [51]. A mutation of the melanocortin 1 receptor (MRC1R), which regulates pigmentation in humans and other vertebrates resulted in decreased melanin synthesis resulting in penetration of more of the less intense solar UVB radiation for the production of vitamin D [51, 53, 54]. Asians with skin type 5 demonstrated very little DNA damage from the same amount of simulated sunlight exposure and were unable to make enough vitamin D in their skin to significantly raise their blood level of 25(OH)D [50]. Therefore the degree of skin pigmentation evolved to protect the skin from the damaging effects from excessive sun exposure while at the same time permitting an adequate amount of vitamin D to be produced. This is nicely demonstrated in Maasai herders who have skin type 6 and have circulating levels of 25(OH)D on average of 48 ng/mL [55]. Achieving these levels requires the ingestion of 3000–5000 IUs daily [56].

The most feared form of skin cancer is melanoma. It has been suggested that the major reason to abstain from any direct sun exposure is for the prevention of this deadly cancer [42]. However it is well documented that most melanomas occur on the least sun exposed areas and occupational sun exposure is associated with a reduced risk. The major risk factors are number of sunburns as a child and young adult, being red headed, having a large number of moles on the body and a genetic predisposition for developing it [48].

There are other numerous studies relating vitamin D deficiency with increased risk for many acute and chronic illnesses. These include increased risk for preeclampsia and the need for a cesarean section, autoimmune diseases including Type 1 and 2 diabetes, multiple sclerosis, cardiovascular disease, infectious diseases, neurocognitive dysfunction, deadly cancers including breast and colon cancers (Fig. 12.14) [29, 30]. What is also remarkable are the earlier observations that living at higher latitudes with less vitamin D producing sun exposure was associated with increased risk for mortality, multiple sclerosis, Type 1 diabetes, hypertension and deadly cancers [7, 30, 41].

Besides the cutaneous production of vitamin D, exposure to solar UVB radiation also increases the production of β-endorphin. Exposure to solar UV radiation is also associated with increased production of nitric oxide and carbon monoxide both of which cause vasodilation and can lower blood pressure. It also increases the expression of the proopiomelanocortin (POMC) gene increase in the production of adrenocorticotropin hormone which helps to regulate the immune system [41].

12.7 Conclusion

There needs to be an acknowledgment by health care officials worldwide that sensible sun exposure is important not only for the production of vitamin D but also for overall health and well-being. A study of Australian dermatologist in the summer revealed that their use of a sunscreen resulted in 87% of them being vitamin D deficient at the end of the summer [57]. The World Health Organization on its website regarding sunlight and health state that some sunlight exposure is important for the production of vitamin D. However time of day, season, latitude, altitude and skin pigmentation all influence the efficiency of the skin to produce vitamin D during sun exposure. An app dminder.info which is free for the iphone and android formats provides guidance for sensible sun exposure and informs to user not only how much vitamin D they can produce when exposed to sunlight but also provides a warning to wear sun protection after that sensible sun exposure to prevent sunburning. For a wide variety of reasons it is not reasonable to expect that you can obtain an adequate amount of vitamin D from sun exposure unless you are outdoors all the time and exposed to a significant amount of your skin to sunlight such as a lifeguard or a Maasai herder or frequent a tanning salon [7, 34, 55, 58]. Following

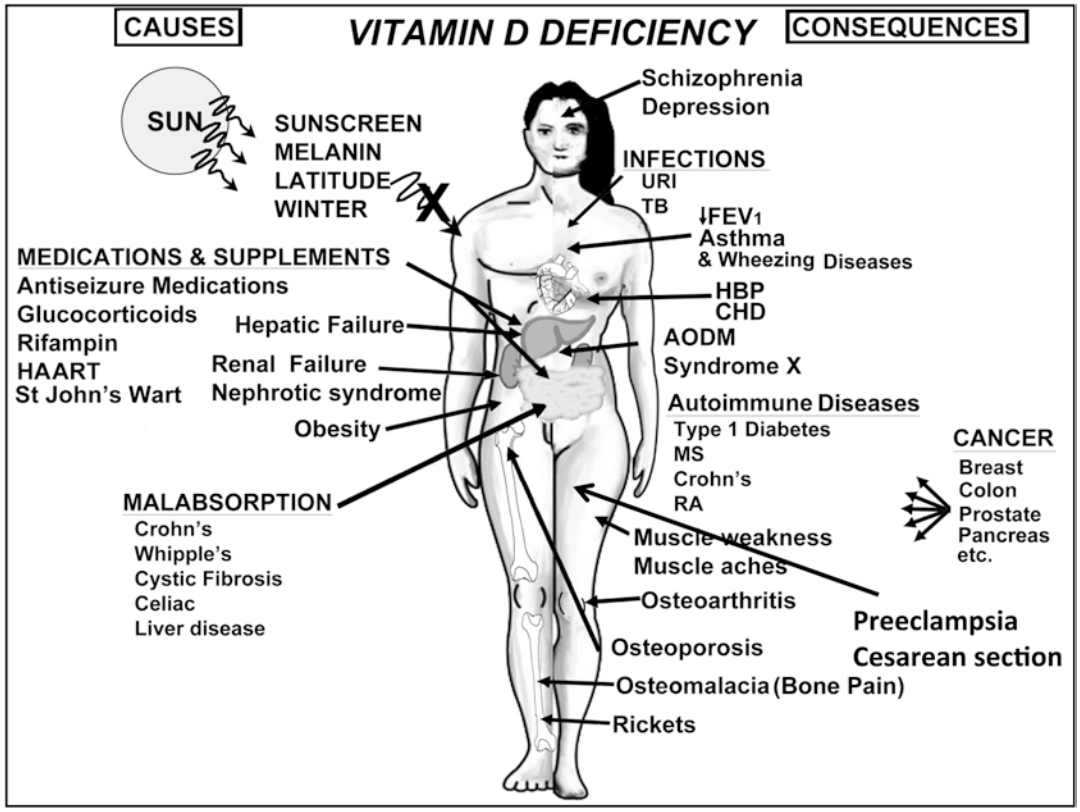

Fig. 12.14 A Schematic representation of the major causes for vitamin D deficiency and potential health consequences (Holick, copyright 2007. Reproduced with permission)

the recommendations of the Endocrine Society will help to achieve blood levels of 25(OH)D in the desired range above 30 ng/mL [45]. The amount recommended are 400–1000 IUs, 600–1000 IUs and 1500–2000 IUs daily for children under 1 year, children 1 year and older and adults respectively. Obese children and adults require 2–3 times more vitamin D to satisfy their requirement. For simplicity I recommend all children can take 1000 IUs daily and teenagers and adults 2000 IUs daily as a supplement. I also recommend that this amount of vitamin D be taken daily throughout the entire year even in the summer. This amount of vitamin D along with any vitamin D available in the diet and sun exposure will not cause vitamin D intoxication [7, 59]. The safe upper level or vitamin D for children is 4000 IUs daily and 10,000 IUs daily for adults as recommended by the Endocrine Society [45].

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