Chapter 27
Vitamin D

Michael F. Holick

Key Points

- Vitamin D, the sunshine vitamin, is well recognized as being important for the development and maintenance of bone health throughout life.
- The major source of vitamin D for children and adults is from sun exposure. Solar ultraviolet B radiation converts 7-dehydrocholesterol to previtamin D_3 which in turn thermally isomerizes to vitamin D_3.
- Vitamin D_3 from the skin enters the circulation and along with vitamin D_2 and vitamin D_3 coming from dietary sources travels to the liver and is converted to the major circulating form 25-hydroxyvitamin D [25(OH)D].
- 25(OH)D enters the circulation and travels to the kidneys where it is converted to its active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2$D interacts with its vitamin D receptor (VDR) in the intestine resulting in an increase in intestinal calcium absorption. In the skeleton it increases the number of osteoclasts to mobilize calcium from the skeleton when necessary.
- Vitamin D deficiency, defined as a 25-hydroxyvitamin D <20 ng/mL and vitamin D insufficiency has been defined as a 25(OH)D of 21–29 ng/mL and sufficiency as >30 ng/mL.
- Vitamin D toxicity is usually not observed until 25(OH)D levels are >200 ng/mL.
- Essentially every tissue and cell in the body has a VDR and many cells including macrophages have the ability to convert 25(OH)D to 1,25$(OH)_2$D.
- Epidemiologic and association studies have suggested that vitamin D deficiency increases risk for many acute and chronic illnesses including autoimmune diseases such as multiple sclerosis and type 1 diabetes, cardiovascular disease, several cancers, type 2 diabetes, infectious diseases and neurocognitive dysfunction.
- The Endocrine Society's practice guidelines recommends children 1 year and older receive 600–1,000 IU daily and adults 1,500–2,000 IU daily with the caveat that obese people require 2–3 times more.

Keywords Vitamin D • Sunlight • 25-Hydroxyvitamin D • 1,25-Dihydroxyvitamin D • Rickets • Osteoporosis • Osteomalacia • Cancer • Autoimmune diseases • Infectious diseases

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27.1 Introduction

Vitamin D, the sunshine vitamin, is well recognized as being important for the development and maintenance of bone health throughout life. The major source of vitamin D for children and adults is from sun exposure. Solar ultraviolet B radiation converts 7-dehydrocholesterol to previtamin D_3 which in turn thermally isomerizes to vitamin D_3. Once formed it enters the circulation and along with vitamin D_2 and vitamin D_3 coming from dietary sources travels to the liver and is converted to the major circulating form 25-hydroxyvitamin D [25(OH)D]. 25(OH)D enters the circulation and travels to the kidneys where it is converted to its active form 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. 1,25(OH)2D interacts with its vitamin D receptor (VDR) in the intestine resulting in an increase in intestinal calcium absorption. In the skeleton it increases the number of osteoclasts to mobilize calcium from the skeleton when necessary. Vitamin D deficiency, defined as a 25-hydroxyvitamin D <20 ng/mL, is one of the most common medical disorders worldwide. Strategies using sensible sun exposure with the app dminder.info along with vitamin D supplementation are discussed in detail. Vitamin D insufficiency has been defined as a 25(OH)D of 21–29 ng/mL and sufficiency as >30 ng/mL. Vitamin D toxicity is usually not observed until 25(OH)D levels are >200 ng/mL. Essentially every tissue and cell in the body has a VDR and many cells including macrophages have the ability to convert 25(OH)D to $1,25(OH)_2D$. Epidemiologic and association studies have suggested that vitamin D deficiency increases risk for many acute and chronic illnesses including autoimmune diseases such as multiple sclerosis and type 1 diabetes, cardiovascular disease, several cancers, type 2 diabetes, infectious diseases and neurocognitive dysfunction. Because vitamin D toxicity is an extremely rare occurrence based on the totality of evidence to date about the many health benefits of vitamin D it is reasonable to encourage sensible sun exposure in combination with vitamin D supplementation. The Endocrine Society's practice guidelines recommends children 1 year and older receive 600–1,000 IU daily and adults 1,500–2,000 IU daily with the caveat that obese people require 2–3 times more.

27.2 Evolution of Vitamin D

Although it is not certain when vitamin D became critically important for calcium metabolism and bone health for our early ancestors, there is evidence that some of the earliest phytoplankton life forms were photosynthesizing vitamin D more than 750 million years ago [1–3]. Life evolved in a fertile soup that contained all of the organic and inorganic compounds necessary for life to evolve. One of the key elements that early life forms used was calcium for regulation of many metabolic processes. As invertebrates and vertebrates evolved, they took advantage of the high calcium content of their ocean environment (approx. 400 mmol) and used it as a major component for their exo- and endoskeletons, respectively. When vertebrate life forms ventured onto land, the calcium on which they became dependent was plentiful in the soils, but they had no mechanism to extract it. Plants, however, extracted the precious calcium out of the soils and distributed it throughout their structures. Thus, calcium was harvested by vertebrates from the soil indirectly by the ingestion of these plants. To utilize the dietary calcium there was a need for a mechanism to recognize the calcium status of the organism and to regulate the efficiency of intestinal calcium absorption depending on the organism's calcium needs. It is likely that vitamin D played a crucial role in early vertebrate development by regulating intestinal calcium absorption and calcium metabolism [1–3].

27.3 Vitamin D Metabolism and Action on the Intestine

Once vitamin D is made in the skin, it enters the circulation. Vitamin D (vitamin D represents either vitamin D_2 or vitamin D_3) from the diet is incorporated in chylomicrons and absorbed into the lymphatic system, where it eventually is deposited into the venous circulation. Both dietary and skin sources of vitamin D are bound in the circulation to a vitamin D-binding protein (DBP) [4]. Some of the lipophylic vitamin D in the circulation is deposited in the body fat, while most of it is directed to the liver [5–7]. Once it enters hepatocytes, it is metabolized by the vitamin D-25-hydroxylase (CYP27A) and transformed to 25-hydroxyvitamin D [25(OH)D] [6, 7]. 25(OH)D leaves the hepatocyte and enters the circulation and is once again bound to the DBP. 25(OH)D is the major circulating form of vitamin D and, as a result, is used to determine the vitamin D status of both children and adults. The 25(OH)D–DBP complex is recognized by megalin that is located in the plasma membrane of the renal tubular cells. Megalin facilitates the endocytic transport of the 25(OH)D–DBP complex into the renal cell [8]. 25(OH)D is then released and enters the mitochondria, where the cytochrome P450-25-hydroxyvitamin D-1-hydroxylase (CYP27B1; 1-OHase) converts it to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] [3, 6, 7] (Fig. 27.1). The renal 1-OHase is upregulated by hypocalcemia and hypophosphatemia. Parathyroid hormone (PTH) is a potent stimulator of the renal 1-OHase whereas fibroblast growth factor 23 (FGF23) produced by osteocytes and osteoblasts inhibits its activity (Fig. 27.1). During pregnancy and lactation, estrogen and prolactin are also thought to play a role in upregulating the 1-OHase [6, 7].

$1,25(OH)_2D$ is considered to be the biologically active form of vitamin D. It binds to its specific nuclear vitamin D receptor (VDR), which in turn binds with the retinoic acid X receptor (RXR) to form a herterodimeric complex. This complex interacts with specific sequences in the promoter region of vitamin D-responsive genes, known as vitamin D-responsive element (VDRE) [3, 7, 9, 10]. The binding of the VDR-$1,25(OH)_2D$-RXR complex to the VDRE initiates the binding of several transcriptional factors that ultimately results in either an increased or decreased expression of vitamin D-responsive genes [9–11].

$1,25(OH)_2D$ is recognized by the VDR in the small intestine, resulting in an increase in the expression of the epithelial calcium channel on the mucosal surface of the intestinal absorptive cell [2, 3, 7]. In addition, there is an increase in the expression of the calcium-binding $protein_{9K}$ (calbindin), calcium-dependent ATPase, and several other brush border proteins [2, 3, 7, 10, 12]. The ultimate result is that $1,25(OH)_2D$ enhances the efficiency of intestinal calcium absorption from a baseline of approx. 10–15 to 30–40 %. Most of the dietary calcium is absorbed in the duodenum and to a lesser extent in the jejunum and ileum.

Once $1,25(OH)_2D$ carries out its function in the small intestine, it then induces the expression of the 25-hydroxyvitamin D-24-hydroxylase (CYP-24). This results in the initiation of a cascade of metabolic steps that culminates in the cleavage of the side chain between carbons 23 and 24 to yield the water-soluble, biologically inactive excretory product, calcitroic acid [3, 7, 10].

27.4 Vitamin D Action on Bone Calcium Mobilization

Although vitamin D is associated with bone health, the principal physiological function of vitamin D is to support the serum calcium within a physiologically acceptable range in order to maintain neuromuscular and cardiac function and a multitude of other metabolic activities [2]. Thus, when dietary calcium is inadequate to satisfy the body's requirement for calcium, this results in vitamin D becoming a catabolic hormone that mobilizes calcium stores from the skeleton.

$1,25(OH)_2D$ increases the removal of calcium from the skeleton by increasing osteoclastic activity. It was originally believed that $1,25(OH)_2D$ interacted with specific nuclear receptors in preosteoclasts

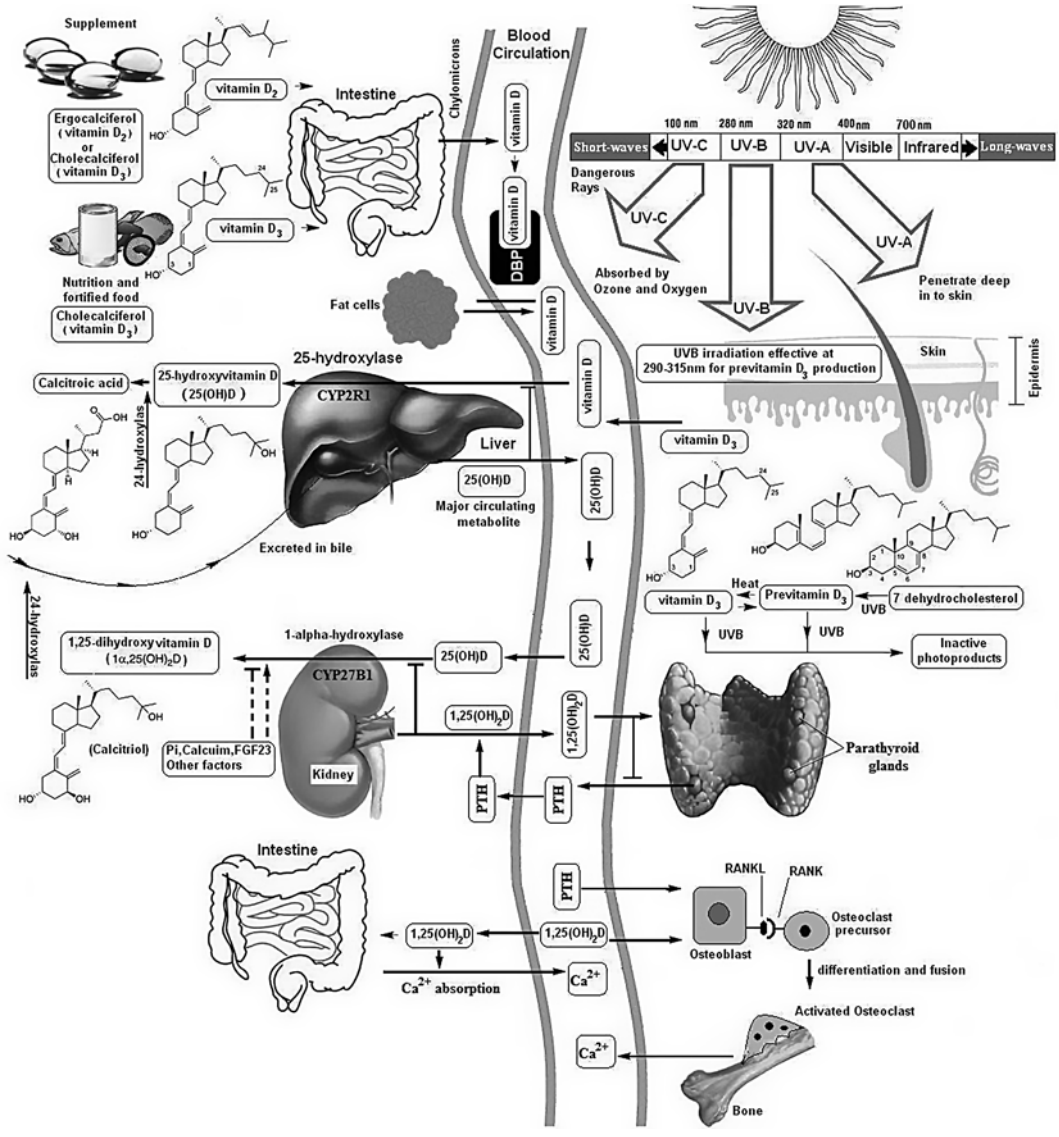


Fig. 27.1 Schematic representation of the synthesis and metabolism of vitamin D for regulating calcium, phosphorus, and bone metabolism. During exposure to sunlight, 7-dehydrocholesterol in the skin is converted to previtamin D_3. Previtamin D_3 immediately converts by a heat-dependent process to vitamin D_3. Excessive exposure to sunlight degrades previtamin D_3 and vitamin 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 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). It 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 factors (FGF-23), and other factors can either increase or decrease the renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. $1,25(OH)_2D$ increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize $1,25(OH)_2D$ to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. $1,25(OH)_2D$ enhances intestinal calcium absorption in the small

to initiate the formation of mature osteoclasts. We now recognize that $1,25(OH)_2D$ initiates the mobilization of preosteoclasts through its interaction with its VDR in osteoblasts. The osteoblast serves as the master cell for regulating bone metabolism. $1,25(OH)_2D$ interacts with the VDR in mature osteoblasts and induces the expression of RANKL (receptor for RANKL) on its plasma membrane surface [3, 7, 13–15]. The precursor monocytic osteoclasts have a membrane receptor for RANKL, known as RANK (receptor activator NFκB). It is the intimate interaction of the preosteoclast's RANK with the osteoblast's RANKL that ultimately signals the preosteoclast to become a mature bone-resorbing multinucleated osteoclast (Fig. 27.1). Thus, in calcium-deficient states $1,25(OH)_2D$ production is enhanced and in turn mobilizes an army of osteoclasts that resorb bone-releasing precious calcium stores into the circulation to maintain ionized calcium levels in the normal range.

27.5 Vitamin D and Bone Mineralization

$1,25(OH)_2D$ interacts with osteoblasts, not only to increase the expression of RANKL, but also to enhance the expression of osteocalcin, alkaline phosphatase, and osteopontin [6, 7, 10, 16, 17]. Despite all of these biological functions in the osteoblast, there is no evidence that $1,25(OH)_2D$ is essential for the ossification process of the collagen matrix [18–20]. This is based on the observation that severely vitamin D-deficient rats that either received a high-calcium and high-phosphorus-with-lactose diet or received calcium intravenously had bones that had no evidence of rickets or other pathology (Fig. 27.2) [19]. This has also been confirmed in rachitic patients with a VDR defect known as $1,25(OH)_2D$-resistant rickets (vitamin D-dependent rickets type 2) and who received an infusion of calcium, resulting in the healing of their rickets [20].

27.6 Dietary Sources of Vitamin D

There are very few foods that naturally contain vitamin D. These foods include oily fish including makerel, eel, and salmon, cod liver oil, sun- and UV-exposed mushrooms, and egg yolks (Table 27.1).

Steenbock [21] recognized the importance of promoting antirachitic activity in foods by irradiating them with ultraviolet radiation. He suggested irradiation of milk that was fortified with ergosterol (provitamin D_2) as a mechanism to provide children with their vitamin D requirement. This recommendation was embraced by the United States, Canada, and Europe, and this simple food fortification program essentially eradicated rickets by 1940.

In the 1930s, the fortification of milk with vitamin D was a novelty and many companies became interested in fortifying their products with vitamin D. This included, among others, Bond bread, Rickter's hot dogs, and Twang soda. Schlitz Brewery cleverly marketed their beer as containing the sunshine vitamin D (Fig. 27.3). In Europe, custards, milk, and other foods were fortified with vitamin D [22].

In the late 1930s, the US Food and Drug Administration forbade any nutritional claims for alcoholic beverages, and vitamin D fortification of beer was halted. In Europe in the 1950s there were

Fig. 27.1 (continued) intestine by stimulating the expression of the epithelial calcium channel (ECaC) and the calbindin 9K (calcium binding protein; CaBP). $1,25(OH)_2D$ is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of the 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. UVB, ultraviolet B. Reproduced with permission from Holick, copyright 2012

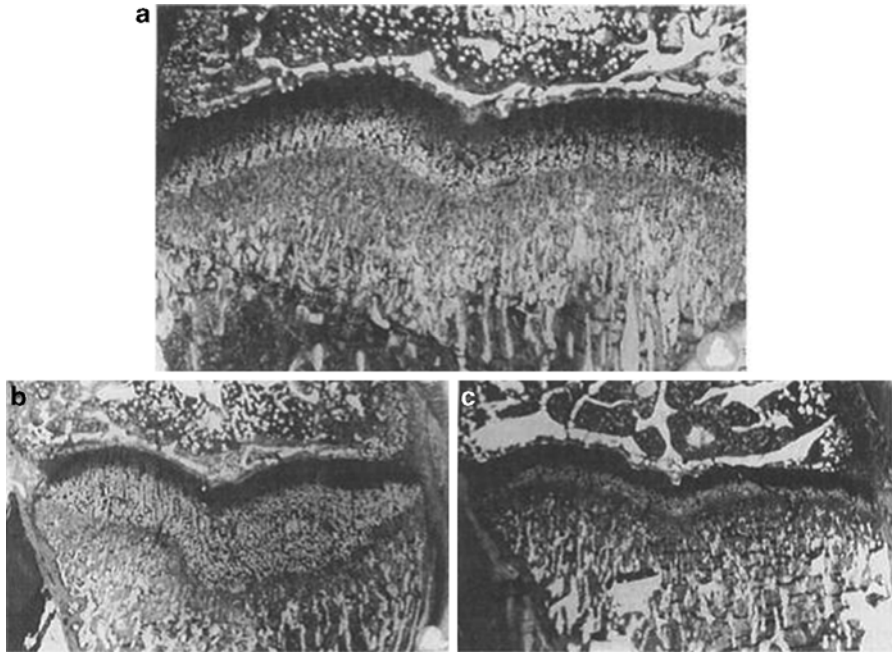


Fig. 27.2 Epiphyseal plates of tibias from rats that were fed (**a**) a vitamin D-deficient diet and supplemented with 125 ng (5 IU) of vitamin D_3 orally five times a week, (**b**) a vitamin D-deficient diet containing 3 % calcium and 0.65 % phosphorus, and (**c**) a vitamin D-deficient diet with 20 % lactose, 4 % calcium, and 1 % phosphorus. Note the wide and disorganized hypertrophic zone in the vitamin D-deficient rat's tibial epiphyseal (**b**) fed high calcium and normal phosphorus diet compared with normal tibial epiphyseal plates from the rats that were either vitamin D repleted (**a**) or maintained on normal serum calcium and phosphorus by being on a high-calcium lactose, high-phosphorus diet (**c**). (Reproduced with permission from ref. [17]

several outbreaks of vitamin D intoxication, that is, hypercalcemia in children, which caused great alarm [23]. This resulted in most European countries forbidding the fortification of any food product with vitamin D.

Based on reports that these infants who were hypercalcemic also suffered from mental retardation, heart problems and had altered facial features is consistent with these children suffering from the rare genetic disorder Williams syndrome. Children with this genetic disorder have elfin faces, heart problems, mild mental retardation and have a hypersensitivity to vitamin D which can cause hypercalcemia. Recently Finland and Sweden have lifted restrictions on the fortification of milk with vitamin D [7].

In the United States, milk, orange juice, some breads, cereals, and yogurts are fortified with vitamin D. There is 100 IU (2.5 μg) of vitamin D in 8 oz of milk. In most European countries, margarine and some cereals are fortified with vitamin D (Table 27.1).

The reason milk was the vehicle for the vitamin D supplementation program was that children drank milk and they were at risk for developing rickets. However, with the awareness that vitamin D deficiency is an epidemic in both young, middle-aged, and older adults, there is a need for other dietary sources of vitamin D other than milk. Tangpricha et al. [24] observed that the fat content in milk does not influence vitamin D bioavailability. They also demonstrated that vitamin D added to orange juice was bioavailable for young and middle-aged adults. Thus, the recent introduction of vitamin D-fortified orange juice and other juice products heralded a new era in the vitamin D fortification process and should have a significant impact on vitamin D status of children and adults who consume these products.

Table 27.1 Sources of vitamin D_2 and vitamin D_3

Source	Vitamin D content
Natural sources	
Cod liver oil	About 400–1,000 IU/teaspoon vitamin D_3
Salmon, fresh wild caught	About 600–1,000 IU/3.5 oz vitamin D_3
Salmon, fresh farmed	About 100–250 IU/3.5 oz vitamin D_3, vitamin D_2
Salmon, canned	About 300–600 IU/3.5 oz vitamin D_3
Sardines, canned	About 300 IU/3.5 oz vitamin D_3
Mackerel, canned	About 250 IU/3.5 oz vitamin D_3
Tuna, canned	About 236 IU/3.5 oz vitamin D_3
Shiitake mushrooms, fresh	About 100 IU/3.5 oz vitamin D_2
Shiitake mushrooms, sun-dried	About 1,600 IU/3.5 oz vitamin D_2
Egg yolk	About 20 IU/yolk vitamin D_3 or D_2
Sunlight/UVB radiation	About 20,000 IU equivalent to exposure to 1 minimal erythemal dose (MED) in a bathing suit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting about 3,000 IU vitamin D_3
Fortified foods	
Fortified milk	100 IU/8 oz, usually vitamin D_3
Fortified orange juice	100 IU/8 oz vitamin D_3
Infant formulas	100 IU/8 oz vitamin D_3
Fortified yogurts	100 IU/8 oz, usually vitamin D_3
Fortified butter	56 IU/3.5 oz, usually vitamin D_3
Fortified margarine	429 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D_3
Pharmaceutical sources in the United States	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid	8,000 IU/cc
Supplemental sources	
Multivitamin	400, 500, 1,000 IU vitamin D_3 or vitamin D_2
Vitamin D_3	400, 800, 1,000, 2,000, 5,000, 10,000, and 50,000 IU

IU = 25 ng

27.7 Vitamin D from Sunlight Exposure

Because very few foods contain vitamin D, most children and adults receive their vitamin D requirement from exposure to sunlight. During sunlight exposure, the solar ultraviolet B photons (UVB; with energies 290–315 nm) penetrate into the epidermis and are absorbed by 7-dehydrocholesterol (provitamin D_3) that resides in the plasma membrane of the epidermal cells [3, 15, 25]. This absorption results in a rearrangement of the double bonds that causes the B ring to open to form previtamin D_3 (Fig. 27.1). Previtamin D_3 exists in two conformeric forms, the *s-cis*, *s-cis* (czc) and its more thermodynamically stable counterpart the *s-trans*, *s-cis* (tzc) conformer (Fig. 27.4). It is only the czc conformer that can undergo rearrangement of its double bonds to form vitamin D_3. In order for the skin to efficiently convert previtamin D_3 to vitamin D_3, the previtamin D_3 is made in the plasma membrane and is locked into the czc conformation, which then can rapidly isomerize to vitamin D_3 [26, 27]. Once formed, this molecule no longer is sterically compatible to reside in the cell's plasma membrane and is released into the extracellular space, where it is picked up in the dermal capillary bed and bound to the DBP (Fig. 27.1).

Unlike vitamin D that is absorbed in the small intestine into the chylomicron fraction, where no more than two-thirds of it is bound to DBP, essentially 100 % of the vitamin D_3 that comes from the

Fig. 27.3 In 1932–1936, Schlitz fortified their beer with vitamin D to market it as a unique nutrient-enriched product. However, in 1937 the FDA forbid any nutrient claims for alcoholic beverages and vitamin D was removed from beer

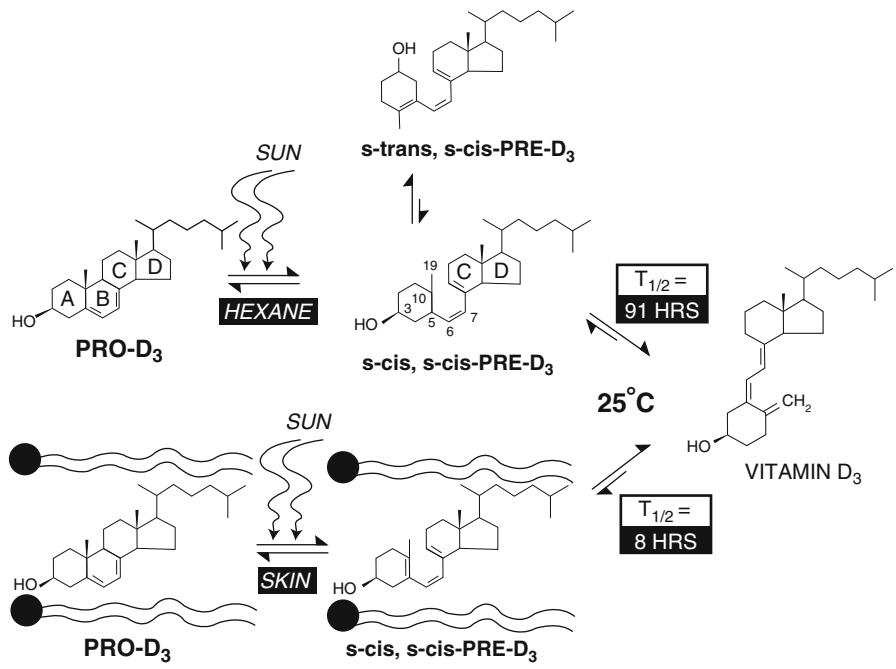


Fig. 27.4 Photolysis of provitamin D_3 (pro-D_3) into previtamin D_3 (pre-D_3) and its thermal isomerization of vitamin D_3 in hexane and in lizard skin. In hexane pro-D_3 is photolyzed to *s-cis*,*s-cis*-pre-D_3. Once formed, this energetically unstable conformation undergoes a conformational change 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 3β-hydroxyl group and the polar head of the lipids, as well as by the van der Waals interactions between the steroid ring and side-chain structure and the hydrophobic tail of the lipids. These interactions significantly decrease the conversion of the *s-cis*,*s-cis* conformer to the *s-trans*,*s-cis* conformer, thereby facilitating the thermal isomerization of *s-cis*,s-*cis*-pre-D_3 to vitamin D_3. (Reproduced with permission from ref. [26])

skin and enters into the venous circulation is bound to the DBP [28]. This gives the cutaneous vitamin D_3 a more prolonged half-life in the circulation and thus provides an advantage for obtaining vitamin D from exposure of the skin to the sun.

27.8 Factors That Influence the Cutaneous Production of Vitamin D_3

Since the vitamin D_3 synthetic process is dependent on the number of UVB photons that enters into the epidermis, anything that interferes with the number of photons reaching the Earth's surface and ultimately penetrating into the viable epidermis results in an alteration in the production of vitamin D_3 in the skin.

During exposure to sunlight, the UVB photons enter into the skin and initiate the photochemistry necessary for producing previtamin D_3. The UVB photons also signal melanocytes to increase the production of melanin. Melanin acts as a natural sunscreen and is efficiently packaged into melanosomes that migrate upward to the upper layers of the epidermis, where they efficiently absorb UVB and ultraviolet A (321–400 nm) radiation. An increase in skin pigmentation is inversely related to the number of UVB photons that can penetrate into the epidermis and dermis. Thus, the efficiency in utilizing UVB photons to produce vitamin D_3 in the skin is inversely related to the amount of skin pigmentation. This effect can be quite dramatic. A person with deep skin pigmentation of African

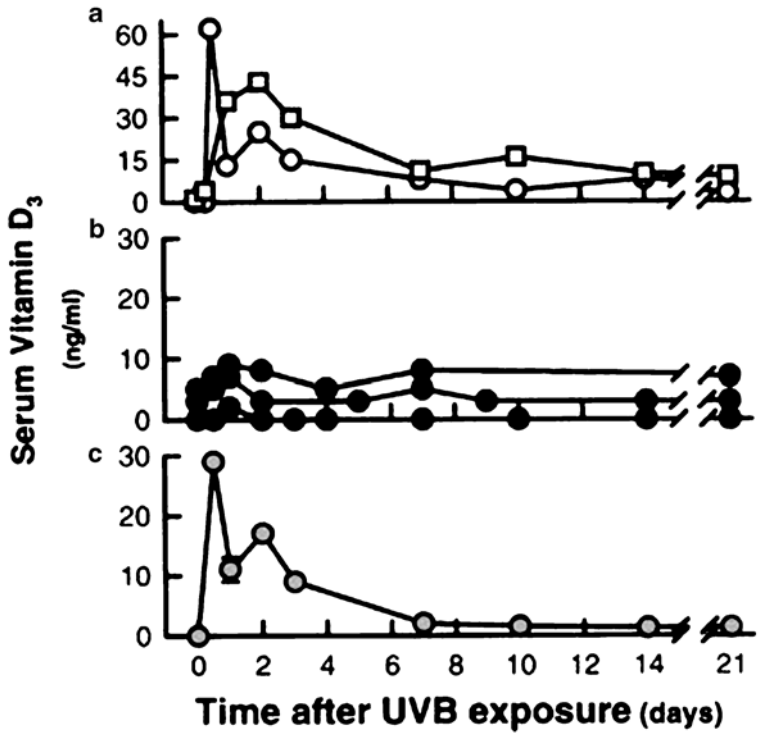


Fig. 27.5 Change in serum concentrations of vitamin D in two lightly pigmented white (skin type 2) (**a**) and three heavily pigmented black subjects (skin type 5) (**b**) after total-body exposure to 54 mJ/cm^2 of UVB radiation. (**c**) Serial change in circulation vitamin D after reexposure of one black subject in **b** to a 320-mJ/cm^2 dose of UVB radiation. (Reproduced with permission from ref. [29]

origin (skin type 5), who is exposed to the same amount of sunlight as a person with minimum skin pigmentation of Celtic or Scandinavian origin (skin type 2), will produce no more than 5–10 % of that produced in the lighter-skinned individual [3, 15, 29] (Fig. 27.5).

Sunscreens are heavily promoted for the prevention of skin cancer and wrinkles. Sunscreens, like melanin, efficiently absorb UVB radiation when applied topically to the skin. As a result, there is a marked diminishment in the penetration of UVB photons into the epidermis. The proper use of a sunscreen (2 mg sunscreen/cm^2 skin surface, i.e., about 1 oz or 25 % of a 4-oz bottle applied to all sun exposed skin of a person wearing a bathing suit) with an SPF of 8 reduces the production of previtamin D_3 by more than 95 % [30] (Fig. 27.6a). Clothing absorbs 100 % of the incident UVB radiation, and thus no vitamin D_3 is made in the skin covered by clothing [31]. This is the reason why women who wear veils and cover all sun-exposed skin with clothing when outside are often vitamin D deficient [32, 33]. Glass also absorbs all UVB photons. Therefore, exposure of the skin from sunlight that has passed through glass will not promote vitamin D_3 synthesis in the skin [34].

Aging causes a decrease in the amount of 7-dehydrocholesterol in the epidermis [7, 34]. Elders exposed to the same amount of sunlight as a young adult will produce approx. 25 % of the amount of previtamin D_3, compared to a young adult [34] (Fig. 27.6b).

The angle by which sunlight penetrates the Earth's atmosphere also dramatically influences the production of previtamin D_3 in the skin. This angle, known as the zenith angle, is related to season, time of day, and latitude. There is a direct relationship with increase in latitude and in the zenith angle of the sun. The higher the zenith angle, the longer is the path length that solar UVB photons have to travel through the ozone layer, which efficiently absorbs most of these vitamin D_3-producing photons.

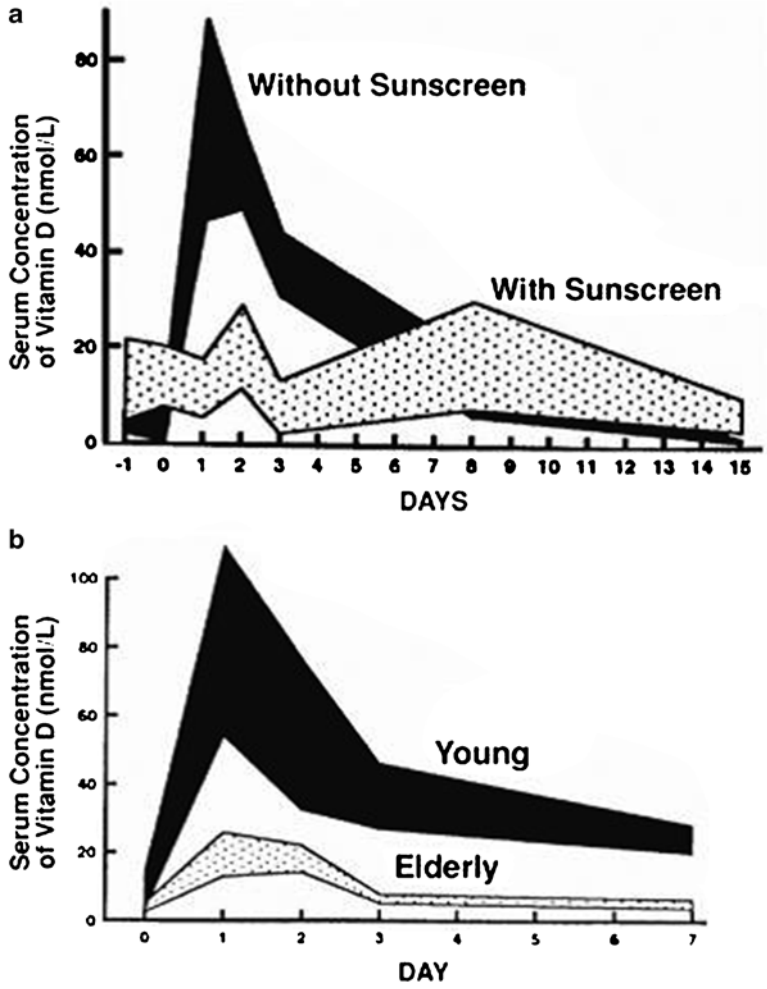


Fig. 27.6 (**a**) Circulating concentrations of vitamin D after a single exposure to 1 minimal erythemal dose of simulated sunlight with either a sunscreen, with a sun protection factor of (SPF-8) 8, or a topical placebo cream. (**b**) Circulating concentrations of vitamin D in response to a wholebody exposure to 1 minimal erythemal dose in healthy young and elderly subjects. (Reproduced with permission from ref. [34]

Typically, in the summer no more than about 0.1 % of the solar UVB photons that hit the outer stratosphere reach the Earth's surface. The lowest zenith angle, which permits more UVB photons to penetrate to the Earth's surface, occurs at around noontime and in the middle of the summer at the Equator.

During the winter (i.e., November–February) above and below 35° latitude, the zenith angle is so oblique that essentially all of the UVB photons are absorbed by the stratospheric ozone layer. As a result, very little, if any, previtamin D_3 can be produced in human skin. At very high latitudes, such as Bergen, Norway, and Edmonton, Canada, little, if any, previtamin D_3 is produced between the months of October and March. Figure 27.7 shows how latitude, season, and time of day dramatically influence the production of previtamin D_3 in the skin [35].

There has been a lot of confusion about the mixed message of avoiding all direct sunlight because of skin cancer risk and the need for some sensible sun exposure to provide children and adults with their vitamin D requirement. Sensible sun exposure which means to never be exposed to an amount of

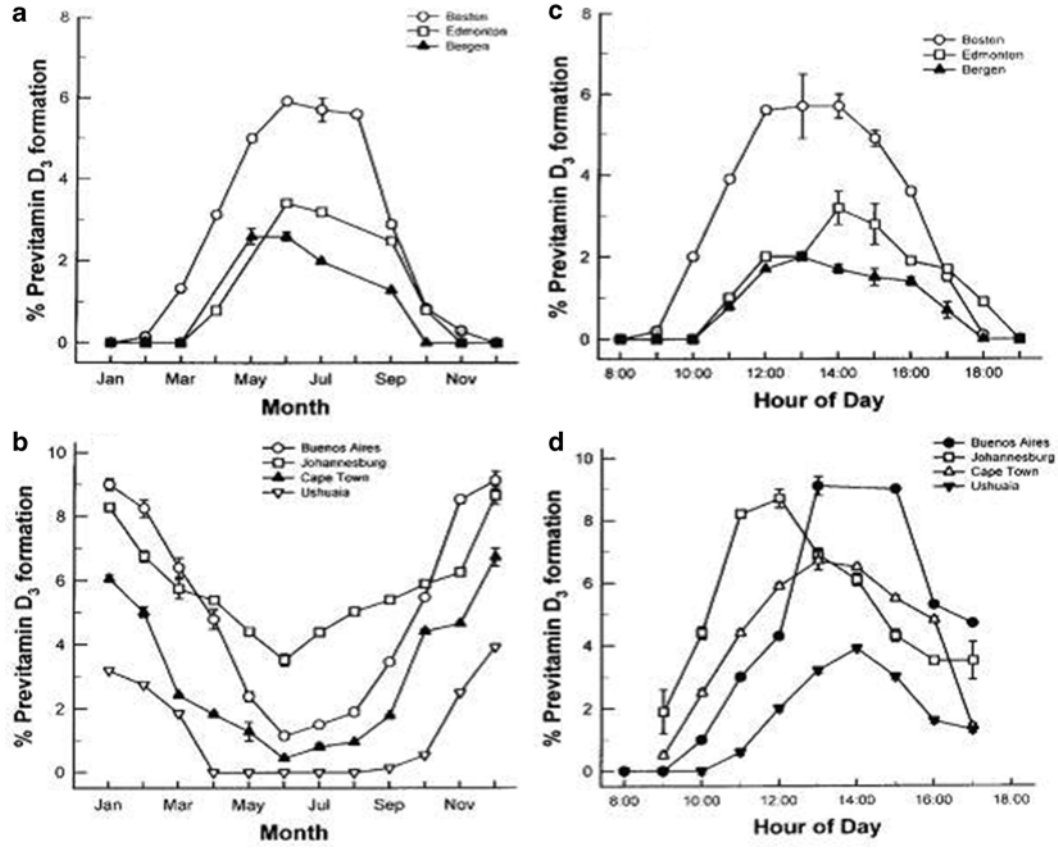


Fig. 27.7 Influence of season, time of day, and latitude on the synthesis of previtamin D_3 in Northern (**a** and **c**) and Southern Hemispheres (**b** and **d**). The hour indicated in **c** and **d** is the end of the 1-h exposure time. (Reproduced with permission from ref. [35]

sunlight that would cause a sunburn, which is the major cause for both skin cancer and skin damage, can provide children and adults with their vitamin D requirement. The recommendation is to always protect the face which is most sun damaged from direct sun exposure. However exposure of other body parts such as arms legs abdomen and back to about 50 % of the time that it would take to get a light pinkness 24 h later (known as one Minimal Erythemal Dose) can be a good source for vitamin D production. To overcome the vagaries of the variables associated with sun-induced vitamin D synthesis including time a day, cloud cover, season, latitude and skin type a free app has been developed that provides the user not only with useful information for how much vitamin D is being produced but also alerts the user when they are at risk for over exposure to sunlight. It is available at dminder.info.

27.9 Consequences of Vitamin D Deficiency on Musculoskeletal Health

Chronic vitamin deficiency in infants and young children causes the bonedeforming disease commonly known as rickets. Vitamin D deficiency disrupts chondrocyte maturation and inhibits the normal mineralization of the growth plates. This causes a widening of the epiphyseal plates that is commonly seen at the ends of the long bones in rachitic children, as well as bulging of the costo-chondral

Fig. 27.8 Typical presentation of two children with rickets. The child in the middle is normal; the children on either side have severe muscle weakness and bone deformities including bowed legs (*right*) or knock knees (*left*)

junctions that results in what is known as the rachitic rosary. The skeleton is also poorly mineralized, due to the low calcium × phosphate product. This poor mineralization makes the skeleton less rigid, and when the rachitic child begins to stand, gravity causes either inward or outward bowing of the long bones in the lower extremities, resulting in bowed legs or knocked knees, respectively (Fig. 27.8).

In adults after the epiphyseal plates have been fused, the skeletal abnormalities resulting from vitamin D deficiency are more subtle. Vitamin D deficiency results in a decrease in efficiency of intestinal calcium absorption. This causes a decrease in the serum ionized calcium, which is immediately recognized by the calcium sensor in the parathyroid glands [36]. This results in an increase in the expression and production of PTH. PTH, in turn, has three options to maintain serum calcium levels within a physiologically acceptable range. It can increase the efficiency of the renal tubules, especially the distal convoluted tubules, to increase the reabsorption of calcium from the ultrafiltrate. It also stimulates the kidney to produce more $1,25(OH)_2D$, which in turn increases intestinal calcium absorption (Fig. 27.1). If these actions are not adequate to maintain the serum calcium levels, then PTH will stimulate the expression of RANKL in osteoblasts to mobilize preosteoclasts to become mature bone-resorbing osteoclasts by a mechanism similar to $1,25(OH)_2D$ [13, 37] (Fig. 27.1). Thus, an increase in osteoclastic activity results in the destruction of the matrix and release of calcium into the extracellular space. The net effect is to increase the porosity of the skeleton, thereby causing a decrease in bone mineral density and precipitating or exacerbating osteoporosis.

A more subtle, but important, effect of PTH on skeletal health is its effect on phosphorus metabolism in the kidney. PTH causes an increase in the urinary excretion of phosphorus. Although subtle in nature, the low-normal or low serum phosphorus is inadequate to maintain a supersaturated level of calcium × phosphorus product, resulting in a mineralization defect of the newly laid-down osteoid by osteoblasts. Histologically this appears as widened osteoid seams (Fig. 27.9) and is known as osteomalacia. Because osteoid has no mineral component, it provides little, if any, structural support to the skeleton and increases risk of fracture [38–41]. In addition, the lack of calcium hydroxyapatite

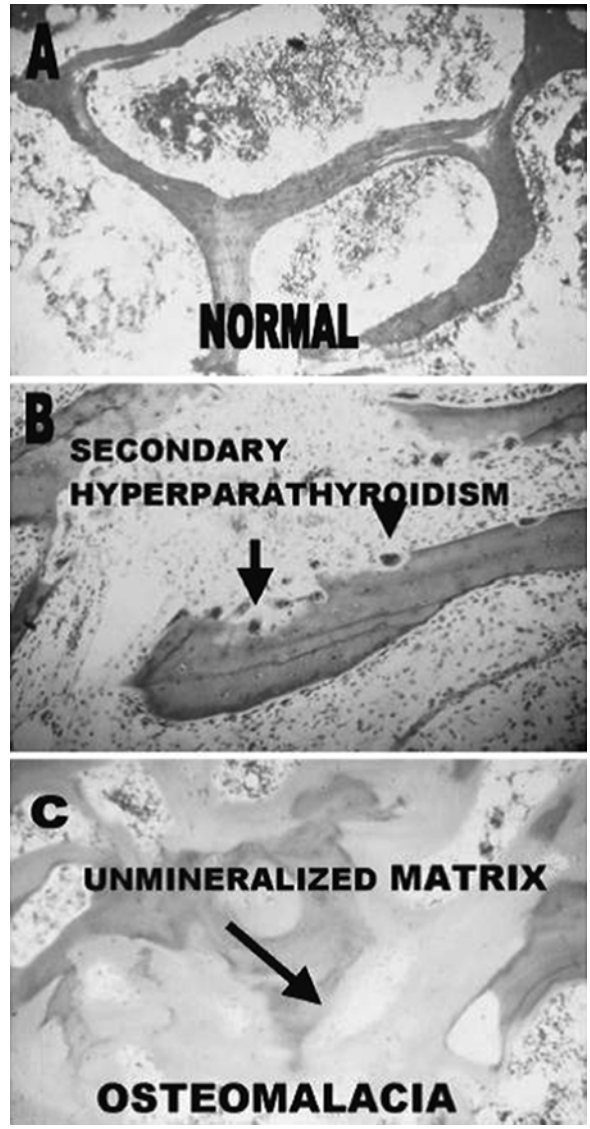


Fig. 27.9 Bone histology demonstrating (**a**) normal mineralized trabecular bone, (**b**) increased osteoclastic bone resorption due to secondary hyperparathyroidism, and (**c**) osteomalacia with widened unmineralized osteoid light gray areas. (Reproduced with permission from ref. [15]

deposition in newly laiddown osteoid results in no increase in bone mineral density. It is not possible to detect either by standard X-rays or bone densitometry the difference between osteoporosis, that is, holes in the skeleton, vs. osteomalacia, which is simply a collagen matrix without mineral [42, 43].

Unlike osteoporosis, which is a silent disease until a fracture occurs, osteomalacia is often associated with bone discomfort. Patients often complain of an aching in their skeleton that is unexplained. This can be detected on physical exam by palpating the sternum with minimum pressure of the thumb or forefinger on the sternum or on the anterior tibia. The patient often complains of discomfort with minimum to moderate applied pressure. Although the exact cause for this pain is not known, its possible that the collagen-rich osteoid that is laid down on the periosteal surface of the skeleton becomes hydrated similar to gelatin in Jell-O and causes an outward pressure on the periostial covering that is innervated with sensory pain receptors [44].

Patients with osteomalacia often complain of muscle aches and muscle weakness. There is mounting evidence that vitamin D deficiency results in muscle weakness and increases sway, which can result in increase in falling, thereby increasing risk of skeletal fractures [33, 45, 46].

Patients often complain to their physicians about nonspecific bone aches, muscle aches, and discomfort. Often after a thorough workup, including a sedimentation rate, rheumatoid factor, and even a bone scan, the physician will inform the patient that no specific cause has been found and often these patients are given the diagnosis of fibromyalgia. It has been estimated that upwards of 40–80 % of patients complaining of nonspecific bone pain and muscle aches and weakness are suffering not from fibromyalgia, but from chronic vitamin D deficiency [33, 44].

27.10 Prevalence of Vitamin D Deficiency in Children and Adults

It is both surprising and alarming that vitamin D deficiency continues to plague both children and adults [7, 38–55] (Fig. 27.10).

Infants who receive their total nutrition from breast feeding are at high risk of vitamin D deficiency because human milk contains very little, if any, vitamin D to satisfy their requirement [53]. This is especially true for infants of color, because their mothers are often vitamin D deficient as well and provide no vitamin D nutrition in breast milk [52, 54]. Even in Caucasian and African American women who had a mean intake of 457 IU/day, the concentrations of vitamin D and 25(OH)D in their milk was 12.6 IU/L and 37.6 IU/L, respectively [7, 53, 54]. It has been estimated that human milk contains no more than about 15 IU of vitamin D in 8 oz.

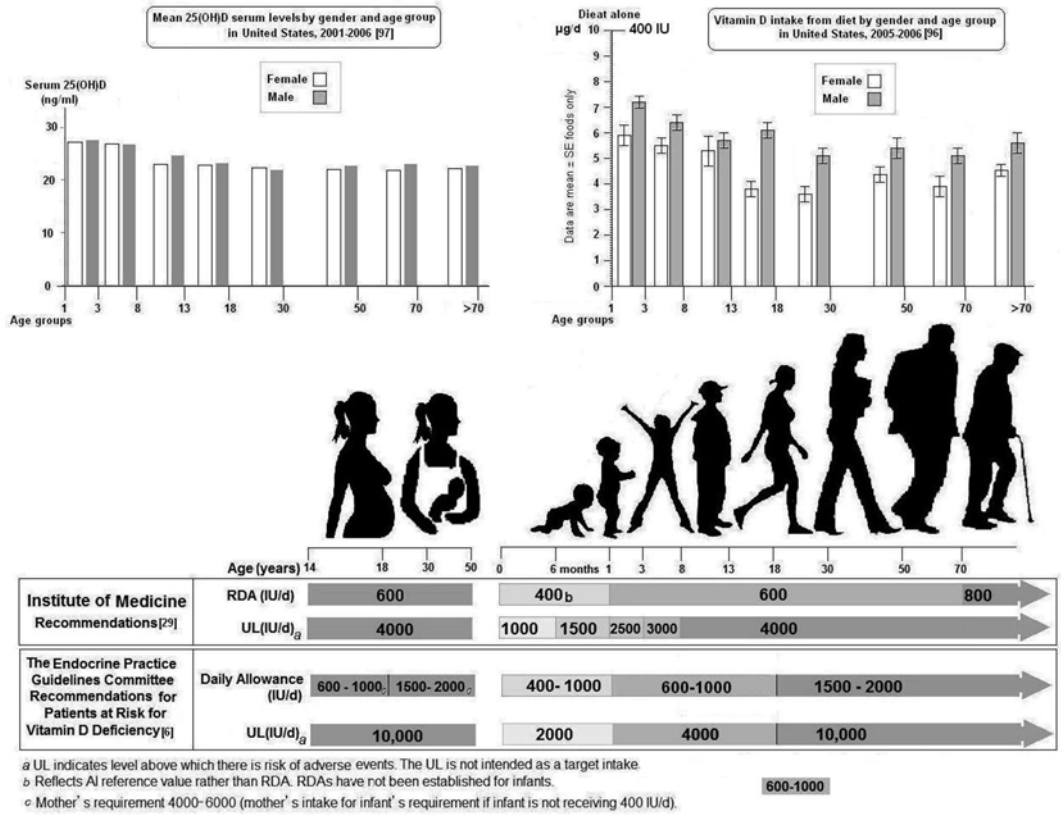


Fig. 27.10 Vitamin D intakes recommended by the IOM and the Endocrine Practice Guidelines Committee. Holick copyright 2012; reproduced with permission

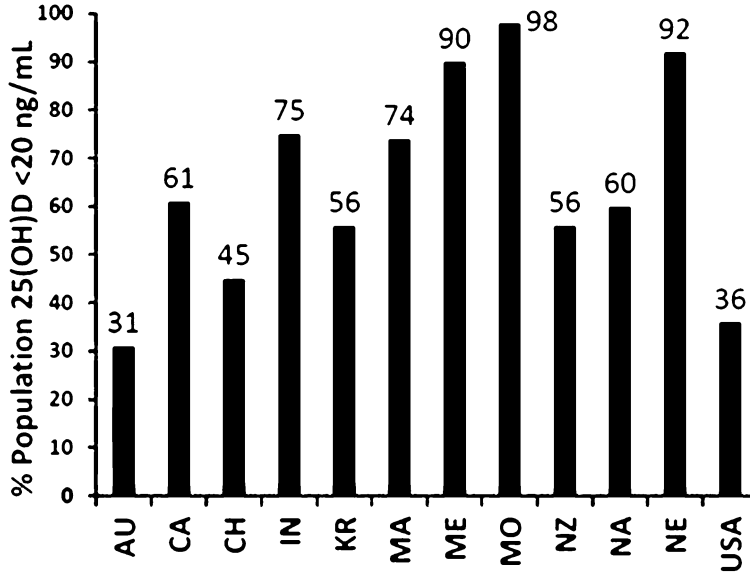


Fig. 27.11 Reported incidence of vitamin D deficiency defined as a 25-hydroxyvitamin D <20 ng/mL around the globe including Australia (AU), Canada (CA), China (CH), India (IN), Korea (KR), Malaysia (MA), Middle East (ME), Mongolia (MO), New Zealand (NZ), North Africa (NA), Northern Europe (NE), United States (USA). Holick copyright 2012; reproduced with permission

Children who are active and outdoors are at little risk of vitamin D deficiency as long as there is a short period of time when they wear no sun protection, such as clothing or sunscreen, on face, arms, and legs.

It has been recognized for more than three decades that globally children and adults are at high risk of developing vitamin D deficiency [7] (Fig. 27.11). Vitamin D deficiency is extremely common in older adults in Europe because essentially no foods are fortified with vitamin D. In the United States and Canada, vitamin D deficiency is also more common than expected [49, 50]. Gloth et al. [47] reported 54 % of community dwellers and 38 % of nursing home residents in the Baltimore area were severely vitamin D deficient [25(OH)D < 10 ng/mL]. Numerous studies have reported that between 25 % and more than 60 % of adults aged 50+ years were vitamin D deficient. In Boston, we observed in independently living elders (83 ± 8 years; 50 white, 14 Hispanic, and 5 African American subjects) in August of 1997 30, 43, and 84 % of white, Hispanic, and black elders were vitamin D deficient [15]. Inpatients are especially at high risk of vitamin D deficiency [55]. It was reported that 57 % of middle-aged and older adults were vitamin D deficient. Sixty percent of the patients consumed less than the recommended adequate intake of vitamin D, and 37 % who had intakes above the recommended daily allowance were found to be vitamin D deficient [7].

It would be expected that young and middle-aged active adults would not be at risk of vitamin D deficiency. However, they have several risk factors for vitamin D deficiency, including long hours of work indoors with little exposure to sunlight, and they are also more likely to wear sun protection on all sun-exposed areas because of their worry about increased risk of skin cancer and wrinkles. As a result, when exposed to sunlight they make little vitamin D_3 in their skin. In Boston, we observed 32 % of medical students and young doctors, aged 18–29 years, were vitamin D deficient [51]. Fifteen percent had secondary hyperparathyroidism, and 4 % of the students and residents remained vitamin D deficient at the end of the summer.

27.11 Causes of Vitamin D Deficiency

The major cause of vitamin D deficiency is that it is not appreciated that very few foods naturally contain vitamin D and that most (80–100 %) of our vitamin D requirement comes from casual exposure to sunlight [7, 15, 56] (Fig. 27.12). Even though oily fish contain vitamin D, it is highly variable depending on what season they were caught and whether they were farm raised and what their vitamin D intake was from their diet. Furthermore, it would require that a person eat oily fish at least 2–3 times a week. To satisfy the vitamin D requirement by drinking milk, would require ingesting six and eight glasses a day for children and adults up to the age of 70, and adults aged 70+ years, respectively [53].

Intestinal malabsorption syndromes, especially of the small intestine where vitamin D is absorbed, can lead to severe vitamin D deficiency [15, 57, 58] (Fig. 27.13). Patients with end-stage hepatic failure not only are unable to produce an adequate amount of 25(OH)D, but often suffer from fat malabsorption and are unable to absorb dietary vitamin D. Patients who are on total parenteral nutrition often suffer from a severe metabolic bone disease that is characteristic of vitamin D deficiency osteomalacia. However, the inclusion of 400 IU of vitamin D in the total parenteral nutrition solution does not protect the patient from vitamin D deficiency bone disease [59, 60].

The principal cause of vitamin D deficiency is lack of adequate exposure to sunlight. The skin has a large capacity to produce vitamin D_3. Exposure of an adult in a bathing suit to simulated sunlight that mimicked the amount of time that would be 1 minimal erythemal dose (1 MED), that is, cause a minimum pinkness to the skin, resulted in an increase in blood levels of vitamin D_3 comparable to ingesting between 10,000 and 25,000 IU of vitamin D [15] (Fig. 27.14). Although aging substantially reduces the amount of 7-dehydrocholesterol in the skin, it still has an adequate capacity to make vitamin D [15, 61–63] (Fig. 27.15).

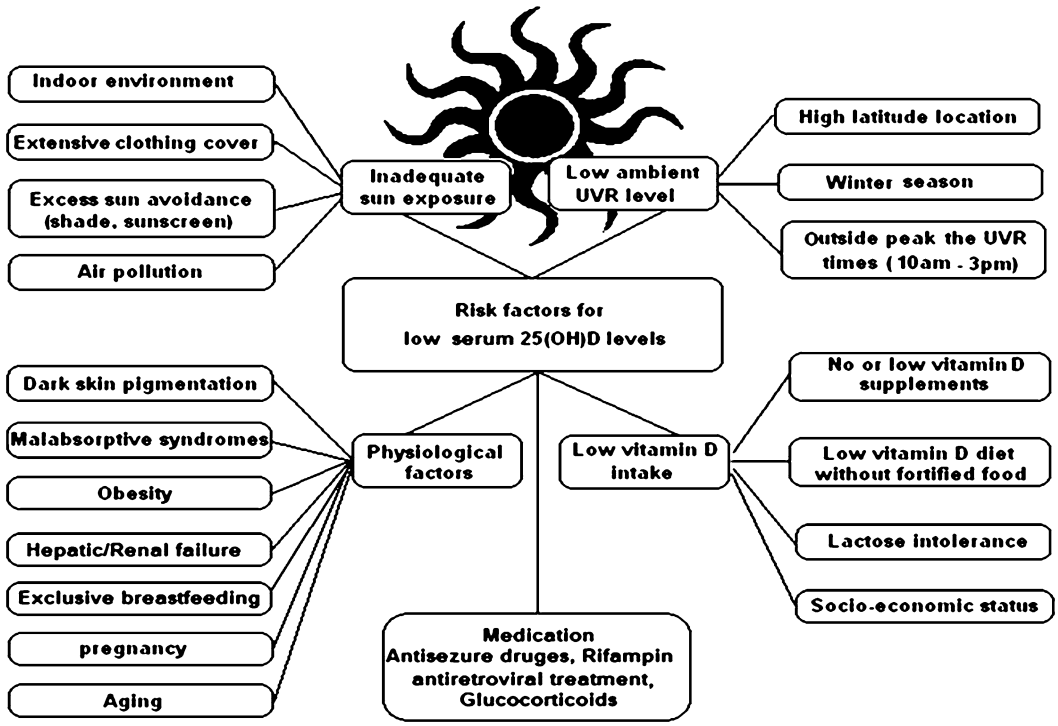


Fig. 27.12 Risk factors of low vitamin D status. Holick copyright 2012; reproduced with permission

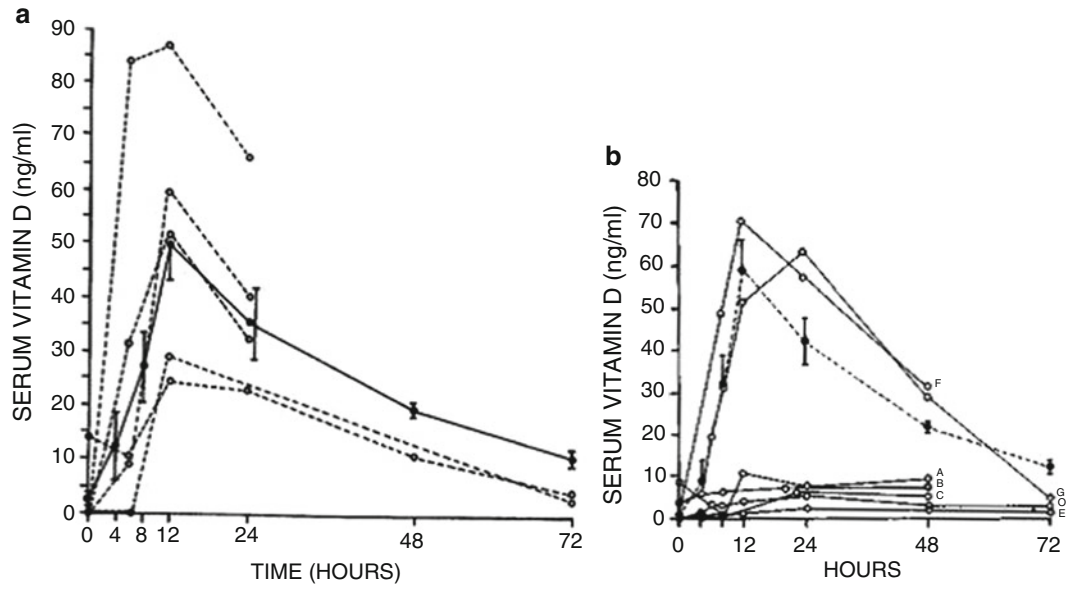


Fig. 27.13 (**a**) Serum vitamin D concentrations in seven patients with intestinal fat malabsorption syndromes after a single oral dose of 50,000 IU (1.25 mg) of vitamin D_2. For comparison, the means and standard errors of vitamin D concentrations measured in seven normal control subjects after a similar dose are indicated by the *filled circles* and *dotted lines*. Note that two patients, one with Crohn's ileocolitis (patient F) and one with ulcerative colitis (patient G), had essentially normal absorption *curves*. Five patients, however, absorbed very little, if any, vitamin D_2. (**b**) Vitamin D absorption in young (*filled circles*) and elderly (*open circles*) adults. Each subject received an oral dose of 50,000 IU of vitamin D_2 and at various times blood determinations were made for circulating concentrations of vitamin D. (Reproduced with permission from ref. [57])

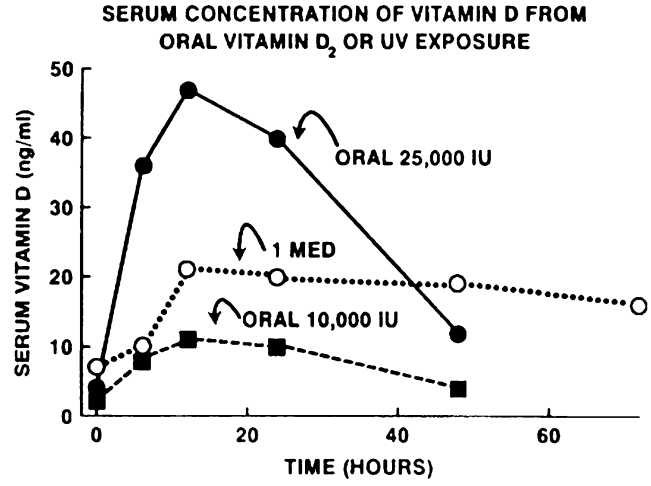


Fig. 27.14 Comparison of serum vitamin D levels after a whole-body exposure to 1 MED (minimal erythemal dose) of simulated sunlight compared with a single oral dose of either 10,000 or 25,000 IU of vitamin D_2. (Reproduced with permission, Holick copyright 2002)

Patients with obesity often complain of bone aches, muscle aches, and weakness, which exacerbates their inability to be active and their obesity. It is recognized that obesity is associated with vitamin D deficiency [5, 64]. This is due to the fact that body fat acts as a sink for vitamin D. Thus, whether vitamin D is produced in the skin or ingested in the diet, a majority of it is deposited in an almost irreversible manner into the body fat and is not bioavailable to the body (Fig. 27.16).

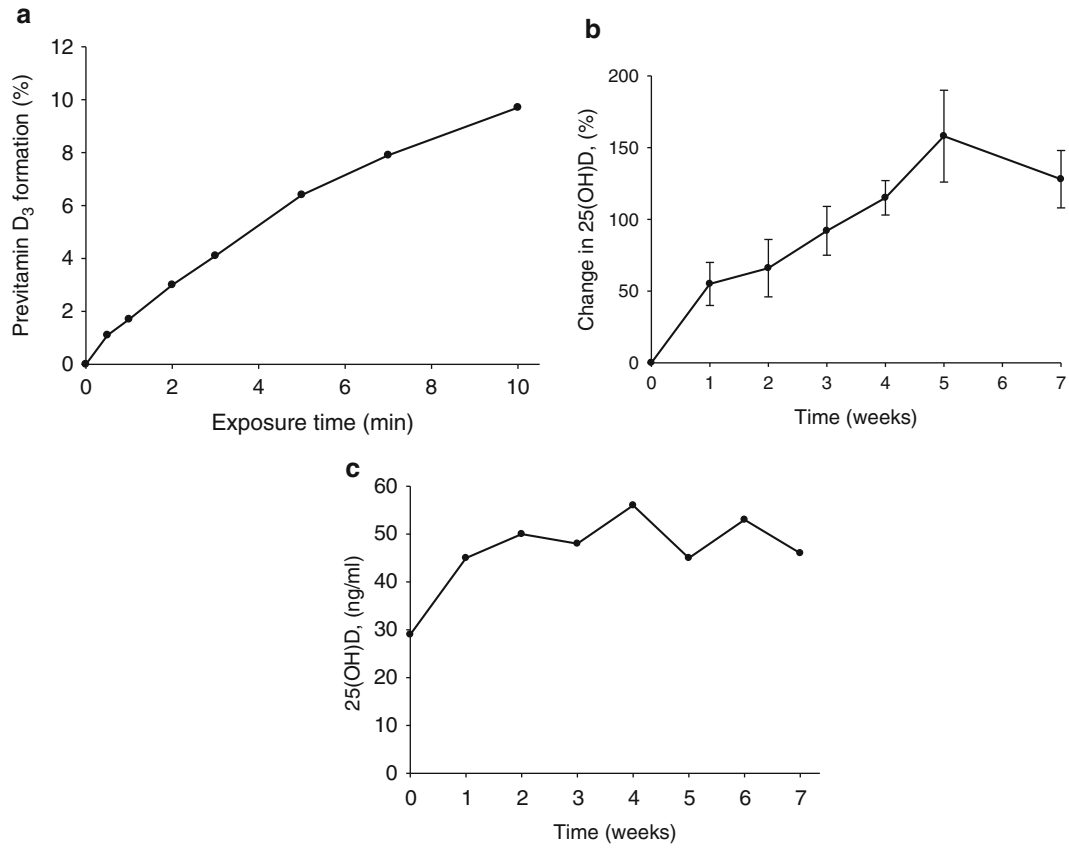


Fig. 27.15 (**a**) Ampoules containing 7-dehydrocholesterol were placed in a tanning bed at various times and conversion of 7-dehydrocholesterol to previtamin D_3 was measured by high performance liquid chromatography. (**b**) Healthy adults were exposed to 0.75 MED in a tanning bed three times a week for 7 weeks. Circulating concentrations of 25(OH)D were determined at baseline and once a week thereafter. (**c**) A 76-year-old healthy male was exposed to tanning bed radiation equivalent to 0.75 MED three times a week for 7 weeks. His circulating concentrations of 25(OH)D were obtained at weekly intervals. Reproduced with permission Holick, M.F., Chen, T.C., Sauter, E.R. Vitamin D and Skin Physiology: A D-Lightful Story. J Bone Miner Res. 2007. 22(S2):V28-V33

27.12 Diagnosis of Vitamin D Deficiency

Often physicians assume that the most sensitive indicator to detect vitamin D deficiency is to observe a below-normal serum calcium value. Unfortunately, as explained previously, the body is vigilant to maintain the serum calcium within the normal range in order to maintain most bodily functions. As a result, a person with vitamin D deficiency develops secondary hyperparathyroidism and maintains serum calcium within the normal range until most available calcium is depleted from the skeleton. The secondary hyperparathyroidism results in mild to moderate hypophosphatemia. However, this is also difficult to detect, especially if the patient's blood is taken in a nonfasting state. Serum phosphorus levels are influenced by dietary phosphorus intake, sugar intake, and by acidosis and alkalosis [6].

With the exception of observing widened epiphyseal plates and Looser's pseudo-fractures in the long bones, it is not possible to detect vitamin D deficiency by X-rays.

The only method to determine vitamin D deficiency is to measure the blood level of the major circulating form of vitamin D, 25(OH)D. Although $1,25(OH)_2D$ is the biologically active form of

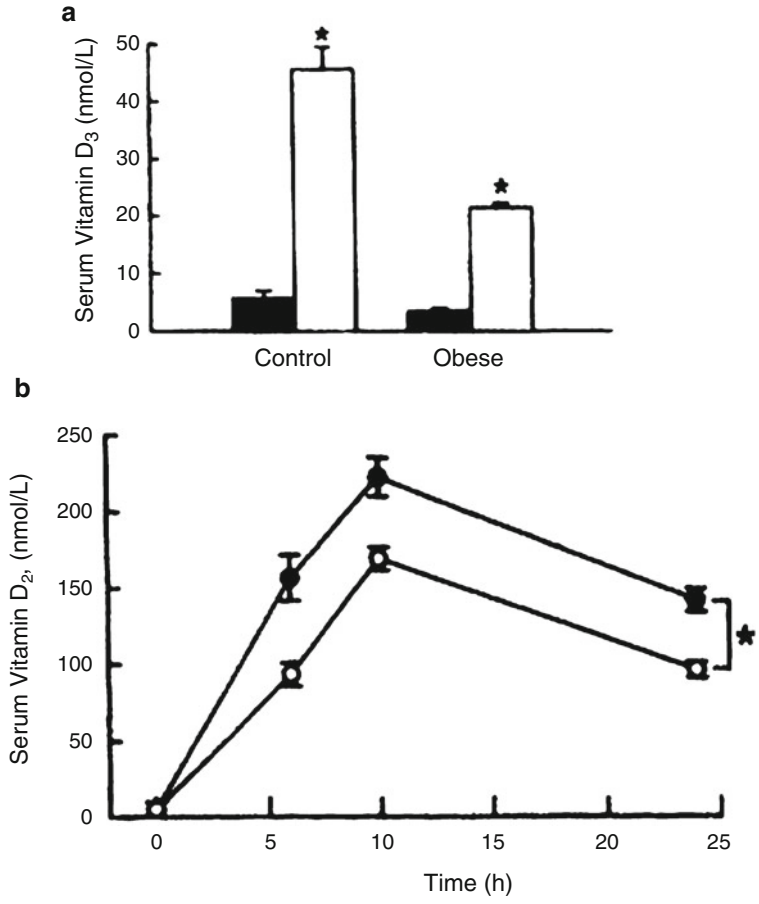


Fig. 27.16 (**a**) Mean (±SEM) serum vitamin D_3, concentrations before (*filled square*) and 24 h after (*open square*) whole-body irradiation (27 mJ/cm^2) with UVB radiation. The response of the obese subjects was attenuated when compared with that of the control group. There was a significant time-by-group interaction, $p = 0.003$. *Significantly different from before values ($p < 0.05$). (**b**) Mean (±SEM) serum vitamin D_2 concentrations in the control (*filled circle*) and obese (*open circle*) groups before and after 25 h after oral intake of vitamin D_2 (50,000 IU, 1.25 mg). Vitamin D_2 rose rapidly until ~10 h after intake and then declined slightly thereafter. *Significant time and group effects by ANOVA ($p < 0.05$) but no significant time-by-group interaction. The difference in peak concentrations between the obese and nonobese control subjects was not significant. (Reproduced with permission from ref. [5])

vitamin D and would appear to be the ideal marker for vitamin D deficiency, it is not. There are several reasons for this. The circulating concentration of $1,25(OH)_2D$ is 1,000th the concentration of 25(OH)D (pg vs. ng/mL). The half-life for $1,25(OH)_2D$ is only 4–6 h, compared to 2 weeks for 25(OH)D [15]. Finally, as a person becomes vitamin D deficient and develops secondary hyperparathyroidism, the kidney's 1-OHase produces more $1,25(OH)_2D$ [3, 6, 7, 15]. Thus, when a patient is vitamin D insufficient there is often a normal or even elevated blood level of $1,25(OH)_2D$ [7, 15, 56]. The measurement of $1,25(OH)_2D$ as a gauge of vitamin D status is not only useless, but often misleads physicians into thinking their patient is vitamin D sufficient since the $1,25(OH)_2D$ levels can be normal.

27.13 Vitamin D Requirement: Adequate Intake vs. Healthy Intake

In 2010, the Institute of Medicine announced the new Recommended Daily Allowances (RDA) for vitamin D (1 μg = 40 IU) for children and adults aged 0–1, 1–70, and 71+ years to be 400, 600, and 800 IU/day, respectively (Fig. 27.10) [53]. In 2011 the Endocrine Society issued its guidelines for the treatment and prevention of vitamin D deficiency. They recommended that children in the first year of life should be receiving 400–1,000 IU daily and children 1 year and older should be receiving 600–1,000 IU daily. For all adults it was recommended that they receive 1,500–2,000 IU daily. They also recommended for those who are obese, i.e. BMI >30, require at least 2–3 times more vitamin D to both treat and prevent vitamin D deficiency [65]. Several investigators have reported on the effect of vitamin D intake on circulating concentrations of 25(OH)D. Vieth et al. [66] gave healthy adults (41 ± 9 years) 4,000 IU of vitamin D a day for 2–5 months and did not observe any untoward toxicity. Their 25(OH)D levels during the winter increased from 10.2 ± 4 to 24.1 ± 4 ng/mL. Barger-Lux et al. [67] evaluated a dose response of vitamin D and 25(OH)D intake in healthy males for 4 and 8 weeks, respectively. The groups of adults treated with 1,000, 10,000, or 50,000 IU of vitamin D_3/day for 8 weeks demonstrated increases in their serum vitamin D_3 levels of 5.0, 52.6, and 300.2 ng/mL, respectively. In the same groups, the 25(OH)D increased by 11.6, 58.4, and 257.2 ng/mL, respectively. Male adults who received 10, 20, or 50 μg of 25(OH)D_3/day for 4 weeks demonstrated increases of 25(OH)D by 11.6, 58.4, and 257.2 ng/mL, respectively. None of the men demonstrated any significant change in either their calcium or 1,25$(OH)_2$D levels. In a follow-up study, Heaney et al. [68] gave 67 men who were in general good health either 0, 25, 125, or 250 μg of vitamin D_3 for approx. 20 weeks during the winter. They observed serum 25(OH)D levels increased in direct proportion to dose with a slope of approximately 0.28 ng/mL for each additional 1 μg of vitamin D_3 ingested. The calculated oral input required to sustain serum 25(OH)D concentrations present in the men during autumn was 12.5 μg/day. The total amount from all sources (supplement, food, tissue stores) needed to sustain the starting 25(OH)D level was estimated at 96 μg (approx. 3,800 IU/day). They concluded that healthy men used between 3,000 and 5,000 IU vitamin D_3/day to meet greater than 80 % of their winter vitamin D requirement that was provided by cutaneous production of vitamin D_3 during the previous spring, summer, and fall (Fig. 27.17).

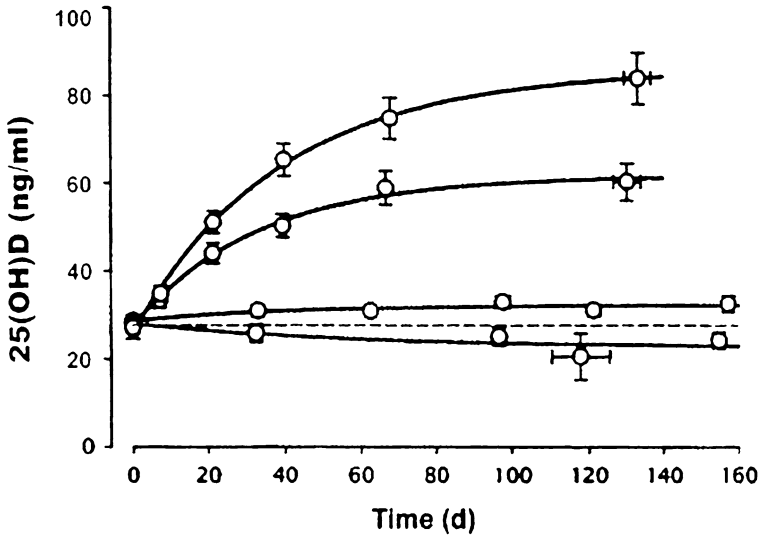


Fig. 27.17 Time course of serum 25-hydroxyvitamin D_3 [25(OH)D] concentration for the four dose groups. The points represent the mean values, and error bars are 1 SEM. The curves are fitted to the mean 25(OH)D_3 values for each dosage group. The curves, from the lowest upward, are for 0.25, 125, and 250 μg vitamin D_3 (labeled dose)/day. The horizontal dashed line reflects zero change from baseline. (Reproduced with permission from ref. [68])

Tangpricha et al. observed that healthy young and middle-aged female and male adults who ingested 1,000 IU of vitamin D/day for 3 months increased their blood levels of 25(OH)D from 15 ± 3 to 38 ± 8 ng/mL after 2 months. Continued intake of 1,000 IU of vitamin D/day did not increase blood levels of 25(OH)D above 40 ng/mL.

27.14 Interpreting Serum 25(OH)D Levels

The normal blood level of 25(OH)D varies from different laboratories, but generally is in the range of 20–100 ng/mL [15, 65]. A normal range for an assay is typically obtained by collecting blood from hundreds of healthy volunteers and then determining the blood level of the analyte and using the mean ± 2 SD as the normal range. Because most healthy volunteers are likely to be vitamin D deficient or insufficient a different strategy has been used to define vitamin D deficiency. This became obvious when Malabanan et. al. [48] reported that healthy adults who received 50,000 IU of vitamin D_2 once a week for 8 weeks along with calcium supplementation had a more than 30 % decline in their PTH values when there blood levels of 25(OH)D were between 11 and 19 ng/mL. No significant change was observed in adults whose blood levels of 25(OH)D were at least 20 ng/mL. The IOM used this data and other observations and concluded that for maximum bone health the 25(OH)D level should be >20 ng/mL. Thus vitamin D deficiency was defined as a 25(OH)D <20 ng/mL [53]. The Endocrine Society also concluded that vitamin D deficiency should be defined as a 25(OH)D <20 ng/mL. They further recommended that vitamin D insufficiency should be defined as a 25(OH)D of 21–29 ng/mL and that vitamin D sufficiency was defined as a 25(OH)D of 30–100 ng/mL with the preferred range of 40–60 ng/mL [65]. These recommendations were based on observations relating serum 25(OH)D with PTH levels. Many studies reported that PTH levels declined and plateaued when a serum 25(OH)D was between 30–40 ng/mL [69]. A study of 675 otherwise healthy German adults who died in an accident had a blood level of 25(OH)D determined and related to bone biopsy that was evaluated for evidence of unmineralized matrix, i.e. osteomalacia, a hallmark of vitamin D deficiency bone disease. The authors concluded that to guarantee no evidence of vitamin D deficiency bone disease that a blood level of 25(OH)D should be at least 30 ng/mL [70].

The upper range of normal by most assays is 80–100 ng/mL. However, this upper normal range is more an estimate than based on any reports of toxicity. Indeed, lifeguards routinely have blood levels of 25(OH)D of 100 ng/mL with no untoward consequences. Heaney et al. [68] observed blood levels of 25(OH)D_3 of 100 ng/mL without any untoward side effects or hypercalcemia. Based on reports of vitamin D intoxication, that is, associated with hypercalcemia, and suppressed PTH levels, 25(OH)D need to be at least 200 ng/mL (Fig. 27.18) [65, 71–74].

Thus, based on the available literature today, it has been suggested that in the absence of any exposure to sunlight, the vitamin D requirement for children and adults is at least 600–1,000 IU and 1,500–2,000 IUof vitamin D/day (Fig. 27.12) [65]. Furthermore, a 25(OH)D level of between 40 and 60 ng/mL should be considered as a healthy range for 25(OH)D [65].

27.15 Treatment for Vitamin D Deficiency

The best method to treat vitamin D deficiency is to give pharmacological doses of vitamin D. This can be accomplished by giving an oral dose of 50,000 IU of vitamin D once a week for 8 weeks [48]. To prevent recurrence of vitamin D deficiency a maintenance dose of 50,000 IU of vitamin D every 2 weeks which is equivalent to ingesting approximately 3,000 IU of vitamin D daily is effective in normal weight adults in maintaining their blood levels of 25(OH)D in the range of 40–60 ng/mL.

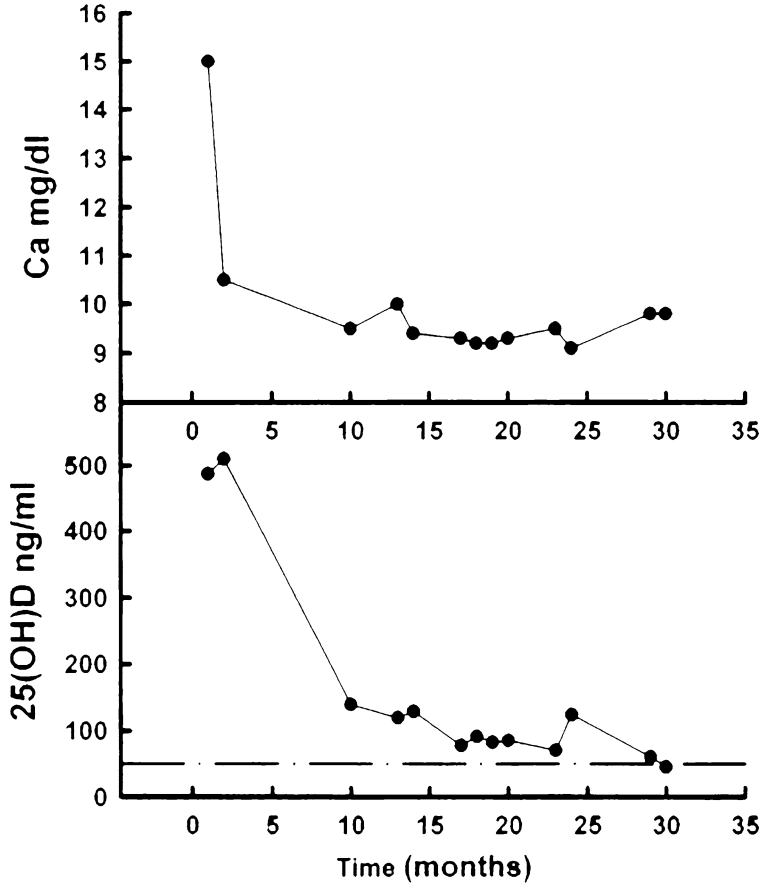
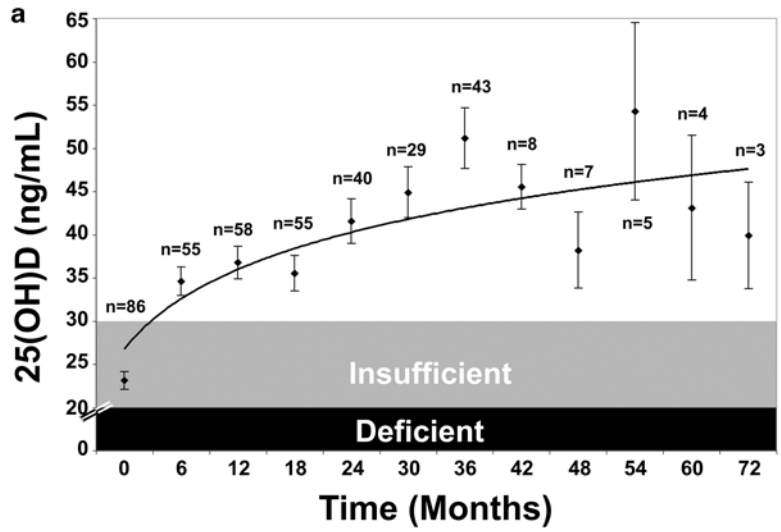


Fig. 27.18 Serum calcium level (*upper panel*) and 25(OH)D level (*lower panel*) in a patient who had vitamin D intoxication after ingestion of an over-the-counter vitamin D supplement that contained as much as one million units of vitamin D_3 in a teaspoon. The patient stopped all vitamin D intake and wore sunscreen before going outside after his hospitalization (month 0). The *dotted line* (*lower panel*) represents the upper limit for the 25(OH)D assay that was 46.7 ng/mL. (Reproduced with permission from ref. [71]

This strategy has been effective for at least 6 years without any toxicity (Fig. 27.19) [75, 76]. Alternatively, intramuscular injection of up to 500,000 IU of vitamin D has been demonstrated to prevent vitamin D deficiency in elderly nursing home residents when given twice a year [77]. However, the intramuscular preparation has been ineffective in many patients in raising blood levels of 25(OH) D when given intramuscularly. This may be a bioavailability problem. In addition, a relatively large volume of oil in which the vitamin D is dissolved when given intramuscularly can be quite uncomfortable, which again is a good reason to give a pharmacological doses of vitamin D orally to correct vitamin D deficiency. Aging does not alter vitamin D absorption [15].

An alternative and an inexpensive method to treat vitamin D deficiency is to encourage patients to be exposed to some sensible sunlight. The amount depends on the person's skin sensitivity, time of day, season of the year, and latitude. For example, for an adult in Boston with a skin type 2, who would get a sunburn after being outside for 30 min at noontime in July, the recommendation is exposure to approx. 30–50 % of that time or 9–15 min 2–3 times a week. Always protect the face because of increased risk of wrinkles or skin damage. Exposure of arms, legs, back, abdomen and legs when possible and using the app dminder.info can provide guidance for sensible sun exposure. No sunscreen or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n=55
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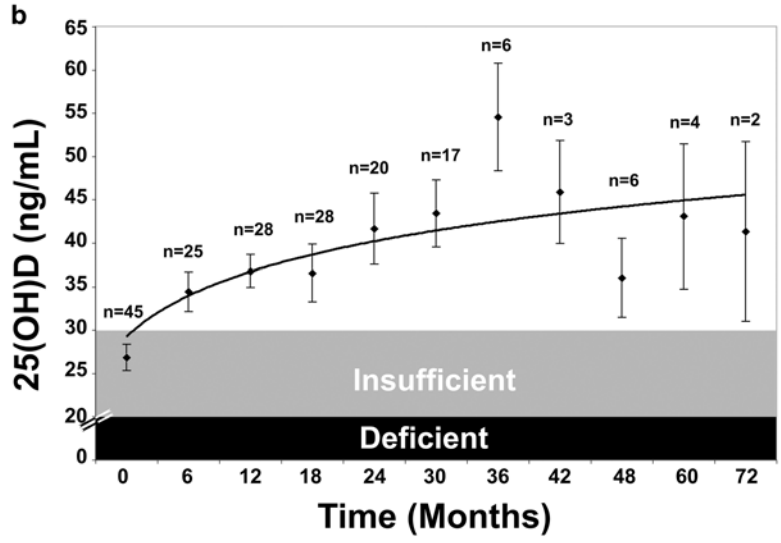
Time (Months)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25(OH)D (ng/mL)
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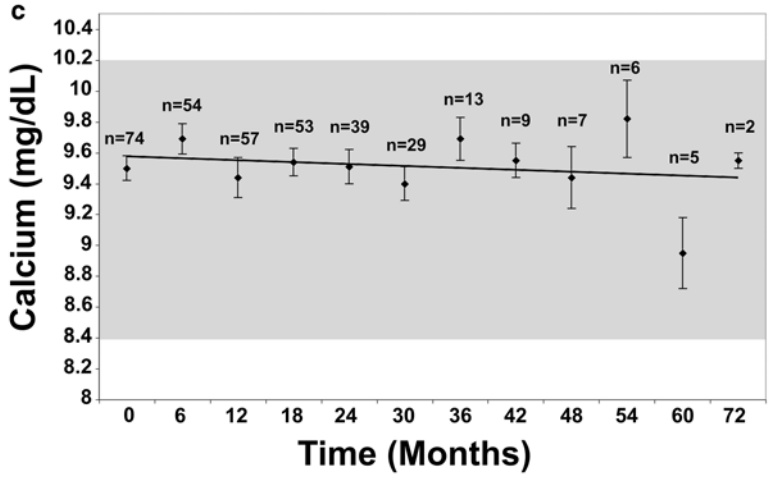
c
Calcium (mg/dL)
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10.2
10
9.8
9.6
9.4
9.2
9
8.8
8.6
8.4
8.2
8
n=74
n=54
n=57
n=53
n=39
n=29
n=13
n=9
n=7
n=6
n=5
n=2
0 6 12 18 24 30 36 42 48 54 60 72
Time (Months)

sun protection should be used for this brief period of time. However, if the person wishes to stay outdoors for a longer period of time, then use of a sunscreen with an SPF of at least 30 and sun protection with clothing is recommended. For those with marked increased skin pigmentation, the time outside could be as much as 30–60 min, again depending on the person's skin sensitivity, time of day, season of the year, and latitude [3, 7, 10, 15, 78].

Patients with severe intestinal malabsorption syndrome and who are on total parenteral nutrition can obtain their vitamin D requirement from sun exposure. However, if they cannot go outside or the season will not permit them to make any vitamin D in their skin, then the use of a UVB radiation source, either a home device or a tanning bed at a tanning salon, would be appropriate. In one patient who had only 2 ft of small intestine left, Koutia et al. [79] reported that exposure to 0.75 MED of tanning bed radiation three times a week markedly increased blood levels of 25(OH)D by 700 % and decreased PTH values into the normal range (Fig. 27.20). In addition, the patient, who suffered from severe bone pain and muscle aches and weakness, had complete relief of her symptoms.

Chuck et al. [62] also have demonstrated that the use of subliminal UVB lighting in an activity room in a nursing home was the most effective means to sustain 25(OH)D levels within the normal range and was far superior to taking a multivitamin that contained 400 IU of vitamin D a day (Fig. 27.21).

27.16 Nonskeletal Consequences of Vitamin D Deficiency

As early as 1941 it was reported that people who lived in higher latitudes were at higher risk of dying of cancer [80]. A multitude of epidemiological studies have now confirmed this early observation [81–89]. There is firm evidence that people living at higher latitudes are at higher risk of developing and dying of breast, colon, ovarian, and prostate cancers [81–87]. Indeed, mortality rates in both men and women are related to their exposure to sunlight [85] (Fig. 27.22).

There is also a latitudinal association with increased risk of developing hypertension and multiple sclerosis [88, 89].

It is now recognized that most tissues and cells possess a VDR. The exact function of $1,25(OH)_2D$ in tissues, such as the brain, breast, prostate, skin, β-islet cells in the pancreas, monocytes, and activated T- and B-lymphocytes, is not fully understood. However, it is known that $1,25(OH)_2D$ is extremely effective in downregulating cellular growth in cells that possess a VDR. Indeed, the potent antiproliferative activity of $1,25(OH)_2D$ has been taken advantage of by the development of activated vitamin D analogs for the treatment of the hyperproliferative disorder psoriasis [90].

Fig. 27.19 (**a**) Mean serum 25-hydroxyvitamin D [25(OH)D] levels in all patients: Includes patients treated with 50,000 IU vitamin D_2 every 2 weeks (maintenance therapy, $N=81$), including those patients with vitamin D insufficiency who were initially treated with 8 weeks of 50,000 IU vitamin D_2 weekly prior to maintenance therapy ($N=39$). Error bars represent standard error of the mean, mean result over 5 years shown. Time 0 is initiation of treatment, results shown as mean values averaged for 6-month intervals. When mean 25(OH)D in each 6-month group was compared to mean initial 25(OH)D, $p<0.001$ up until month 43; $p<0.001$ when all remaining values after month 43 were compared to mean initial 25(OH)D. (**b**) Mean serum 25(OH)D levels in patients receiving maintenance therapy only: Levels for 37 patients who were vitamin D insufficient (25[OH]D levels <30 ng/mL) and five patients who were vitamin D sufficient (25[OH]D levels ≥30 ng/ml) who were treated with maintenance therapy of 50,000 IU vitamin D_2 every 2 weeks. Error bars represent standard error of the mean, mean result over 5 years shown. Time 0 is initiation of treatment, results shown as mean values averaged for 6-month intervals. When mean 25(OH)D in each 6-month group were compared to mean initial 25(OH)D, $p<0.001$ up until month 37; $p<0.001$ when all remaining values after month 43 were compared to mean initial 25(OH)D. (**c**) Serum calcium levels: Results for all 81 patients who were treated with 50,000 IU of vitamin D_2. Error bars represent standard error of the mean. Time 0 is initiation of treatment, results shown as mean values averaged for 6-month intervals. Normal serum calcium: 8.5–10.2 mg/dL. (Reproduced with permission from ref. [75])

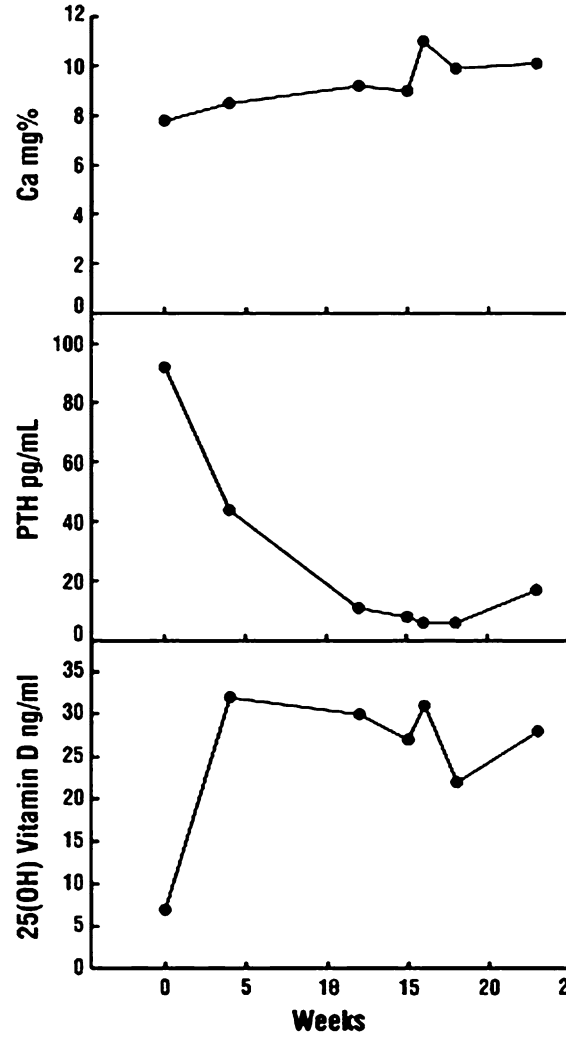

Fig. 27.20 Serum 25(OH)D, PTH, and calcium levels in a patient with Crohn's disease who had whole-body UVB exposure for 10 min, three times in a week for 6 months. (Reproduced with permission from ref. [77])

It is recognized that the β-islet cells have a VDR and that $1,25(OH)_2D$ modulates insulin production and secretion [3, 7, 10]. $1,25(OH)_2D$ also modulates the immune system by regulating the activity of both activated T- and B-lymphocytes and activated macrophages [7, 10, 15, 91, 92]. This may be the explanation for why Hyponnen et al. [93] observed that children treated with at least 2,000 IU of vitamin D a day reduced their risk of developing type 1 diabetes by 80 %. This was similar to what was observed when NOD mice, which invariably develop type 1 diabetes, received $1,25(OH)_2D_3$ [91, 92]*:* they showed an 80 % reduction in developing the disease.

The kidney is an endocrine organ for producing $1,25(OH)_2D$ for regulating calcium metabolism. Recently, it was recognized that $1,25(OH)_2D$ also downregulates the production of renin in the kidney [94]. This may be the explanation for why vitamin D deficiency is associated with hypertension and increased risk of coronary artery disease and congestive heart failure [44, 95–99]. Krause et al. [97] reported that exposure of hypertensive adults to a tanning bed that emitted UVB radiation raised the blood levels of 25(OH)D by more than 100 % and controlled their hypertension. A similar group of hypertensive adults exposed to a similar tanning bed for 3 months that emitted UVA but no UVB radiation not only did not increase their blood levels of 25(OH)D, but also had no effect on their hypertension (Fig. 27.23).

Fig. 27.21 Exposure of nursing home residents to ultraviolet-B lamps that were installed near the ceiling in the day room. This was found to be the most effective method of maintaining serum 25(OH)D levels in these residents. (Reproduced with permission from ref. [62]

27.17 Vitamin D and the Cancer Connection

Although in the 1990s there were several reports that some of the most common cancers occurred in people living at higher latitudes and that colon cancer and prostate cancer rates were significantly reduced in individuals with higher circulating levels of 25(OH)D, it was difficult to understand how increased exposure to sunlight could impact on decreasing risk of common cancers.

The reason for this is that it was well known that any significant increase in vitamin D intake or exposure to sunlight did not raise blood levels of $1,25(OH)_2D$. Thus, it was difficult to understand how increasing one's 25(OH)D levels would be able to regulate cellular growth and prevent some cancers, since circulating levels of $1,25(OH)_2D$, the antiproliferative hormone, were not increased. The mystery was solved when it was observed that prostate cells and prostate cancer cells expressed a functional 1-OHase similar to what was observed in the skin [3, 15, 99–101]. Since this initial observation, it is now recognized that normal colon tissue and colon cancer, breast and breast cancer cells, as well as variety of other cell types have the enzymatic machinery to convert 25(OH)D directly to $1,25(OH)_2D$ [3, 15, 16, 102–104]. Thus, it appears that when 25(OH)D levels are adequate, probably above 30 ng/mL, it acts a substrate for the extra renal 1-OHase in these tissues. The local production of $1,25(OH)_2D$ may be necessary to maintain and regulate genes responsible for cellular growth and to prevent the cells from becoming autonomous, that is, carcinogenic. It has been suggested that once it carries out its function, it induces the 25-hydroxyvitamin D-24-hydroxylase, which in turn catabolizes $1,25(OH)_2D$ to the inactive water-soluble calcitroic acid (Fig. 27.1).

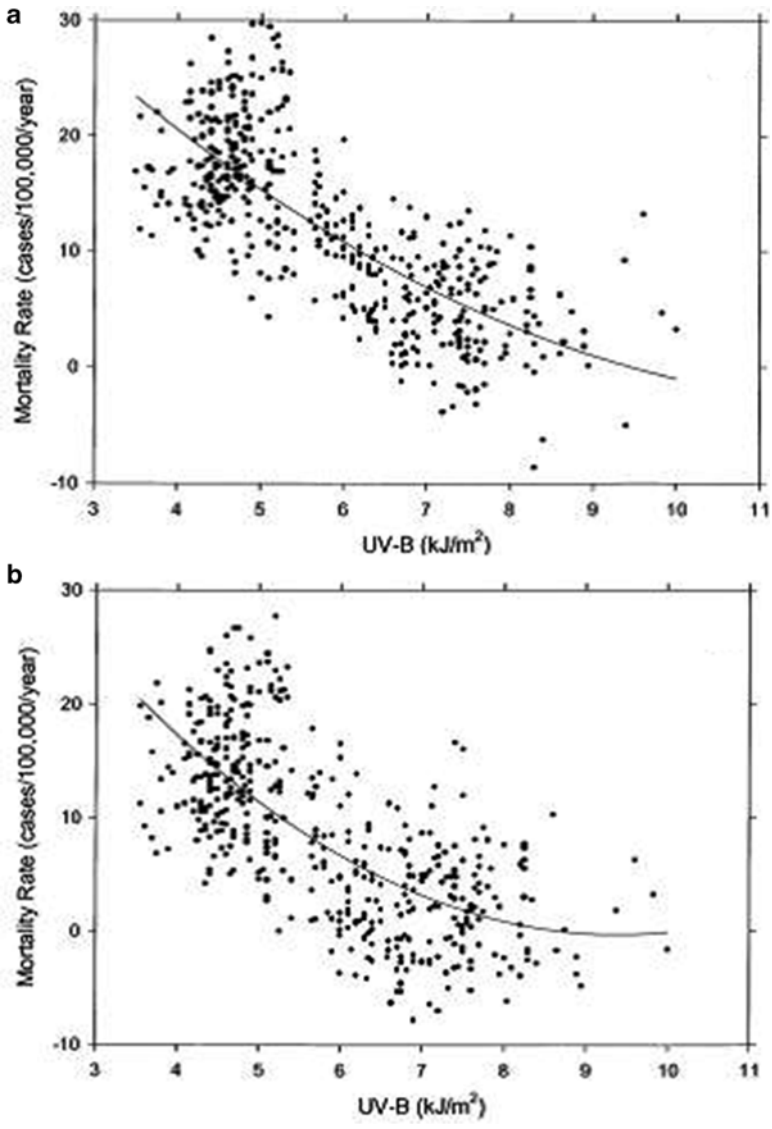

Fig. 27.22 (**a**) Premature mortality due to cancer, white females, vs. total ozone mapping spectrometer (TOMS), July 1992, DNA-weighed UV-B. (**b**) Premature mortality due to cancer with insufficient UV-B, white males, U.S., 1970–1994, vs. July 1992 DNA-weighted UV-B radiation. (Reproduced with permission from ref. [85])

27.18 Conclusion

Vitamin D deficiency is extremely common and needs to be recognized. Vitamin D deficiency in children and teenagers can result in poor bone health and the inability to attain the genetically predetermined peak bone mass. In young, middle-aged, and older adults, vitamin D deficiency causes osteomalacia and can precipitate and exacerbate osteoporosis. In addition, many of the symptoms associated with vitamin D deficiency mimic fibromyalgia, and as a result, many patients go undiagnosed.

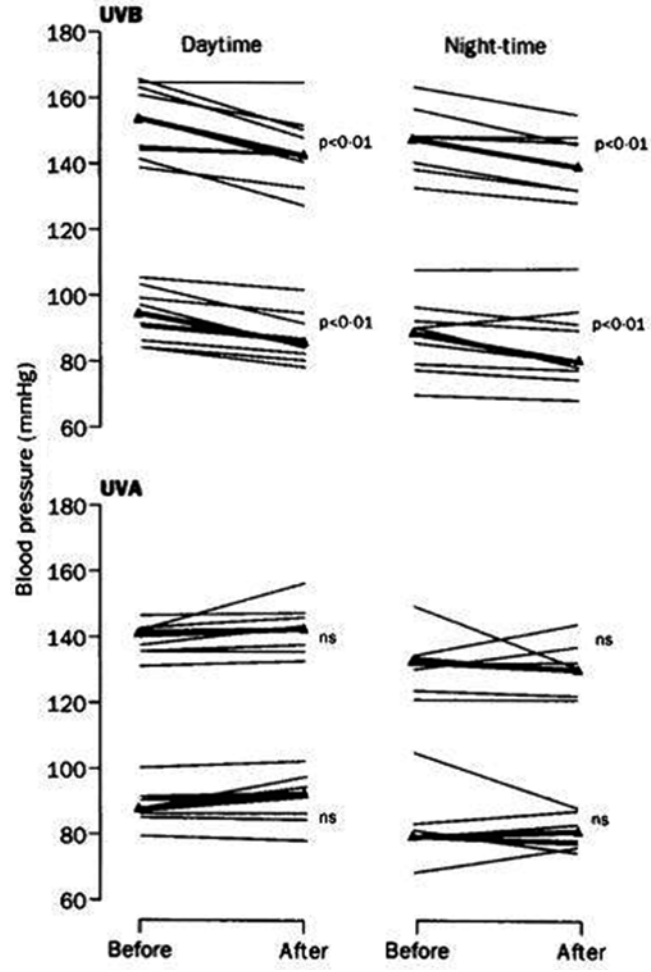

Fig. 27.23 Effect of UV-B and UV-A irradiation on ambulatory daytime and night-time blood pressure in hypertensive adults. *ns* nonsignificant. *Thick line* = mean. (Reproduced with permission from ref. [97]

Vitamin D deficiency, however, may have extremely important health consequences that heretofore have not been fully appreciated. Maintenance of an adequate 25(OH)D level of at least 20 ng/mL and preferably 40–60 ng/mL throughout life may help reduce the risk of developing many chronic diseases, including type 1 diabetes, hypertension, multiple sclerosis, infectious diseases, and cancers of the breast, prostate, colon, and ovary. Vitamin D deficiency has also important health implications for pregnant women and their newborns [7] (Fig. 27.24).

Thus, there needs to be a reawakening about the appreciation of maintaining a healthy vitamin D status throughout life. The best method to determine vitamin D adequacy is to measure 25(OH) D. Similar to evaluating patients for their blood pressure and blood lipid profile on their yearly exam, they should also be evaluated with a 25(OH)D to measure their vitamin D status. This will ensure vitamin D health and mitigate the consequences of vitamin D deficiency.

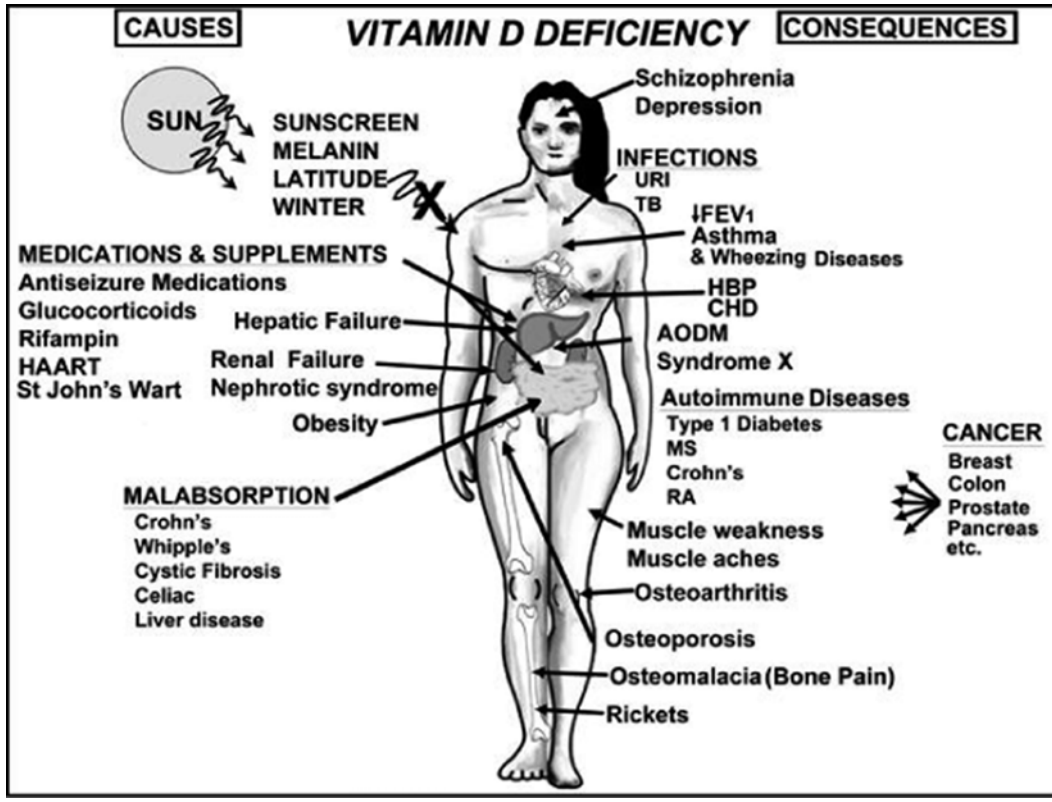

Fig. 27.24 A schematic representation of the major causes for vitamin D deficiency and potential health consequences. Holick copyright 2010. Reproduced with permission

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