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The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention

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Abstract Vitamin D deficiency and insufficiency is a global health issue that afflicts more than one billion children and adults worldwide. The consequences of vitamin D deficiency cannot be under estimated. There has been an association of vitamin D deficiency with a myriad of acute and chronic illnesses including preeclampsia, childhood dental caries, periodontitis, autoimmune disorders, infectious diseases, cardiovascular disease, deadly cancers, type 2 diabetes and neurological disorders. This review is to put into perspective the controversy surrounding the definition for vitamin D deficiency and insufficiency as well as providing guidance for how to treat and prevent vitamin D deficiency.

Keywords Vitamin D deficiency · Vitamin D insufficiency · Sunlight · Rickets · Vitamin D_2 · Vitamin D_3 · 25-hydroxyvitamin D · Vitamin D toxicity

1 Definition of vitamin D deficiency and insufficiency

Up until 1998 vitamin D deficiency was defined as a blood level of 25-hydroxyvitamin D [25(OH)D]; which represents a total concentration of both 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3] of less than 10 ng/mL (25 nmol/L). This definition was mainly based on reports relating blood levels of 25(OH)D and the development of rickets. [1] It was also recognized that vitamin D deficiency was associated with an increase in the circulating levels of parathyroid hormone (PTH). It had been reported that there is an inverse relationship with serum PTH levels and 25(OH)D levels and that the PTH levels began to plateau at approximately 30 ng/mL. [2] Malabanan et al. [3] in 1998 reported that when healthy adults who had blood levels of 25(OH)D of 11–25 ng/mL were given 50,000 IUs of vitamin D_2 once a week for 8 weeks they observed a statistically significant decline in the blood levels of PTH for the adults who have blood levels of 25(OH)D between 11 and 19 ng/mL. There was no significant change in the PTH levels for the adults who had levels of 25(OH)D between 20 and 25 ng/mL. Thus the definition for vitamin D deficiency was redefined in 1998 as a blood level of 25(OH)D < 20 ng/mL [3].

Since 1998 there have been several studies reporting on serum PTH levels as they relate to serum 25(OH)D levels. Thomas et al. reported in the hospital population that PTH levels continued to decline and plateaued when 25(OH)D were approximately 30 ng/mL. [4] In over 1500 postmenopausal women that were evaluated throughout the United States it was observed that PTH levels continued to decline and began to plateau at approximately 30 ng/mL. [5] It reported that women who had a blood level of 21–24 ng/mL had a 3 times higher likelihood of having secondary hyperparathyroidism compared to women who had a blood level of 25(OH)D > 30 ng/mL. (Fig. 1) Valcour et al. reported that age had an independent influence on serum 25(OH)D levels and that there continued to be a decline in PTH levels even when serum 25(OH)D were as high as 70 ng/mL [6] similar to what was previously observed [5].

In 2011 the Institute of Medicine (IOM), after an extensive review of the literature, came to the conclusion that for maximum bone health, a blood level of 25(OH)D of 20 ng/mL and above was adequate [7]. This was based on several observations including those by Malabanan et al.(3) and Priemel et al. [8] Priemel et al. [8] had collected bone biopsies and blood

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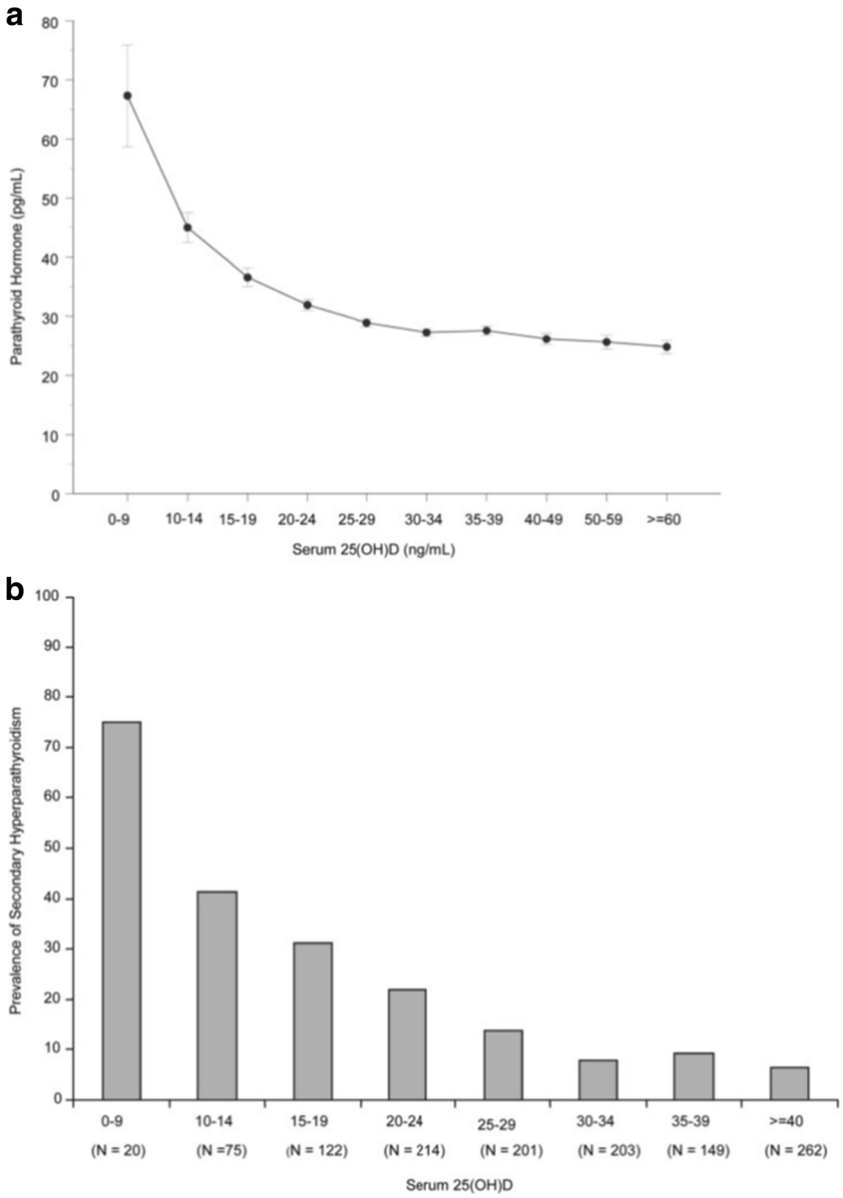


Fig. 1 A, Mean (+ − SE) serum PTH (picograms per milliliter) by serum 25(OH)D subgroups. Subject PTH concentrations (picograms per milliliter) relative to serum 25(OH)D concentrations sorted by subgroups delineated by predefined cutoffs for analyses of 25(OH)D inadequacy. Serum PTH values began to increase with 25(OH)D concentrations less than 29.8 ng/ml. B, Percent of subjects with secondary hyperparathyroidism by 25(OH)D level. The percent of subjects with secondary hyperparathyroidism sorted by subgroups with serum 25(OH)D concentrations delineated by predefined cutoffs for analyses of 25(OH)D inadequacy. (ref 5, Reproduced with permission)

from 675 German adults between the ages of 20–90 years who died in an accident. They related evidence for osteomalacia, based on wide unmineralized osteoid seams in the bone biopsies with their blood levels of 25(OH)D. The authors concluded that remarkably upwards of 25% and 35% of these otherwise presumed healthy German adults had evidence of vitamin D deficiency osteomalacia and osteoidosis respectively. They further concluded that when the adults had a blood level of 25(OH)D of at least 30 ng/mL there was no evidence of vitamin D deficiency bone disease based on the bone biopsies demonstrating no evidence for osteomalacia or osteoidosis. The IOM reviewed the Priemel data in detail and incorrectly concluded that less than 1% of adults in the study who had blood levels of 25(OH)D between 21 and 29 ng/mL had evidence of vitamin D deficiency osteomalacia and therefore concluded that a blood level of 20 ng/mL was adequate for bone health [7].

The Endocrine Society in 2011 reported on the findings from their assembled panel of vitamin D experts. In the published Endocrine Society's Practice Guidelines on Vitamin D, vitamin D deficiency was defined as a 25(OH)D < 20 ng/mL, insufficiency as 21–29 ng/mL and sufficiency as at least 30 ng/mL for maximum musculoskeletal health. [9] They also recognized the several studies reporting on the inverse relationship with serum PTH levels and serum 25(OH)D levels whereby most but not all studies [5, 6] reported that PTH levels begin to plateau when 25(OH)D levels were at approximately 30–40 ng/mL. In addition the expert panel evaluated the Priemel et al. [8] data. They realized that when you take the number of presumed healthy adults with evidence of

osteomalacia and who had a blood level of 25(OH)D between 21 and 29 ng/mL and divide it by the number of adults who also had blood levels of 25(OH)D between 21 and 29 ng/mL it was determined that not less than 1% as suggested by the IOM but 24% of these German adults had evidence of vitamin D deficiency osteomalacia [9, 10]. In addition the Endocrine Society's Practice Guidelines Committee conducted a meta-analysis on vitamin D status and falls and concluded that a blood level of 25(OH)D of at least 30 ng/mL was required to reduce risk for falls [9, 11]. Therefore the Committee recommended that for maximum musculoskeletal health that the blood level of at least 30 ng/mL for serum 25(OH)D should be considered to be vitamin D sufficient. This definition has also been accepted by the National Osteoporosis Foundation, International Osteoporosis Foundation, American Association for Clinical Endocrinologists, and the American Geriatric Society [12, 13].

2 The vitamin D deficiency pandemic

Vitamin D deficiency and insufficiency is a global health problem [12–27]. (Fig. 2) Pregnant women, people of color (blacks, Hispanics and anyone with increased skin melanin pigmentation), obese children and adults and children and adults who practice abstinence from direct sun exposure are at especially high risk [9, 25, 27]. A prospective study conducted in Boston in 40 pregnant women who were documented to be ingesting on average 600 IUs of vitamin D daily throughout their pregnancy (the RDA for vitamin D recommended by the IOM for all adults including pregnant women up to the age of 70 years) reported that 76% of the mother's and 81% of the newborns were vitamin D deficient by having a blood level of 25(OH)D < 20 ng/mL [28]. Vitamin D deficiency during pregnancy increases risk for preeclampsia, the need for a cesarean section as well as wheezing disorders and dental caries in their offspring [9, 25, 29–31]. Most pregnant women especially in China, India, Middle East, Central and South America and Africa do not receive a prenatal vitamin which usually contains 400–600 IUs of vitamin D. However since 600 IUs of vitamin D daily is inadequate to sustain serum 25(OH)D above 20 ng/mL this explains a multitude of reports worldwide that pregnant women are at high risk for being vitamin D deficient throughout the pregnancy even if they're taking a prenatal vitamin; in some countries up to 100% have been reported to be vitamin D deficient [25].

Vitamin D deficiency and insufficiency is common in children worldwide. Even in the United States where milk and some juices and cereals are fortified with vitamin D, 50% of children ages 1–5 and 70% of children ages 6–11 had a 25(OH)D < 30 ng/mL [32]. (Fig. 3) It was concluded that this was caused by a decrease in milk consumption, wearing sun protection during sun exposure and increased incidence of obesity [33]. High prevalence of vitamin D deficiency and

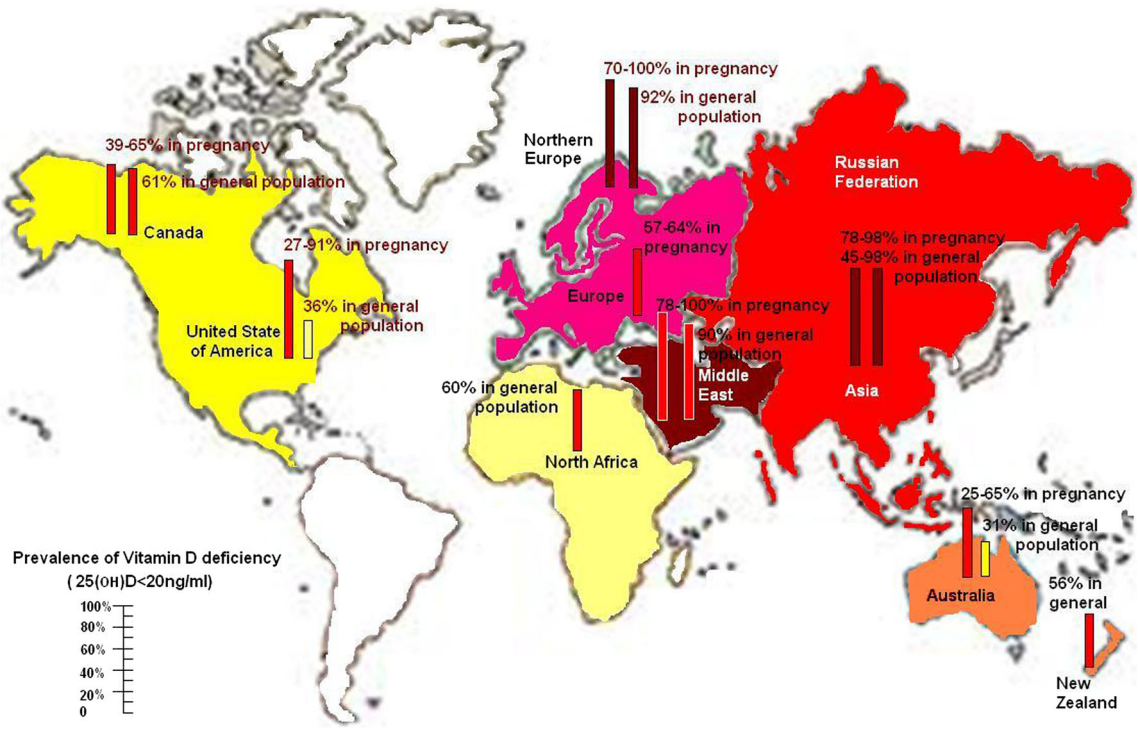


Fig. 2 Reported incidence of vitamin D deficiency defined as a 25-hydroxyvitamin D level below 20 ng/ml around the globe in pregnant women and general population. (Holick copyright 2013, reproduced with permission)

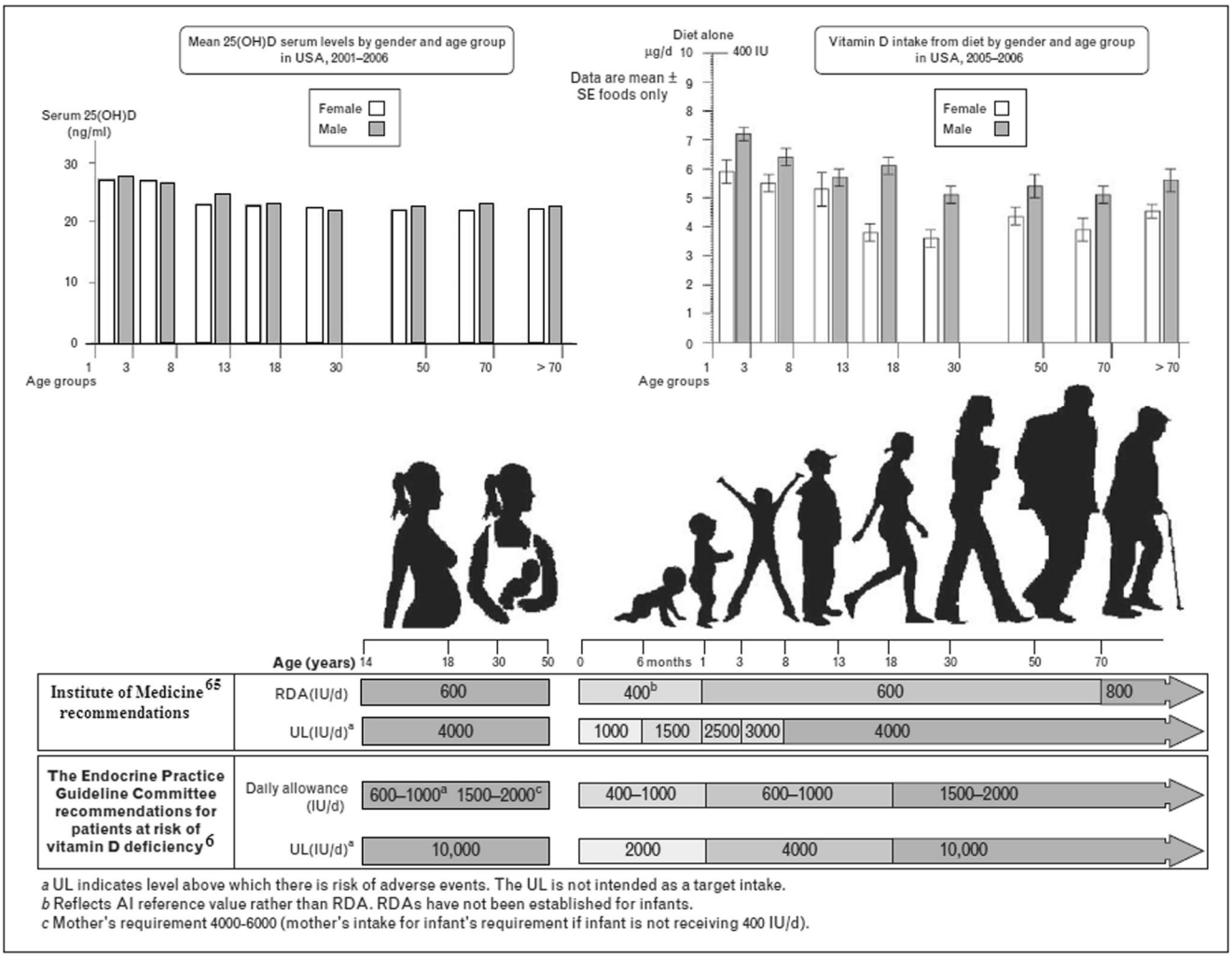


Fig. 3 Serum 25-hydroxyvitamin D levels and vitamin D intakes in children and adults in the United States. Vitamin D intakes recommended by the IOM and the Endocrine Society Practice Guidelines Committee. IOM, Institute of Medicine. (Holick copyright 2013, reproduced with permission)

insufficiency has been documented in Europe,China, India, Middle East and South America where foods are not fortified with vitamin D [13, 15, 18, 23–26].

It has been estimated that approximately 30% and 60% of children and adults worldwide are vitamin D deficient and insufficient respectively [24]. Even in Australia it was reported at 31% (22% in men and 39% in women) of adults had a blood level of 25(OH)D < 20 ng/mL and 73% less than 30 ng/mL [24].

3 Causes for the vitamin D deficiency pandemic

The major cause for the vitamin D deficiency pandemic is the lack of appreciation that sun exposure has been and continues to be the major source of vitamin D for most children and adults [33–35]. (Fig. 4) Very few foods naturally contain vitamin D. These include oily fish such as salmon, mackerel and herring, mushrooms exposed to sunlight or that are sun-dried and cod liver oil [1, 25, 34]. Some, and sometimes substantial, vitamin D in the form of 25(OH)D is present in meat including beef and pork [36, 37]. Many chickens, pigs, and cows are increasing their muscle content of 25(OH)D_3 due to the addition of 25(OH)D_3 into various animal feeds. Civilizations living in far northern and southern latitudes obtain dietary sources of vitamin D not only from oily fish but also from blubber from seals and whales as well as polar bear liver [34].

Sunlight exposure remains the major source of vitamin D for most children and adults [33–35]. During sun exposure 7-dehydrocholesterol, the immediate precursor in the cholesterol biosynthetic pathway, absorbs ultraviolet B radiation (290–315 nm) resulting in breaking of the bond between carbon 9-carbon 10 to produce previtamin D_3. Once formed this thermodynamically unstable seco-steroid undergoes a rearrangement of its triene system to form the thermodynamically stable vitamin D_3. Once formed it travels to the liver where it is

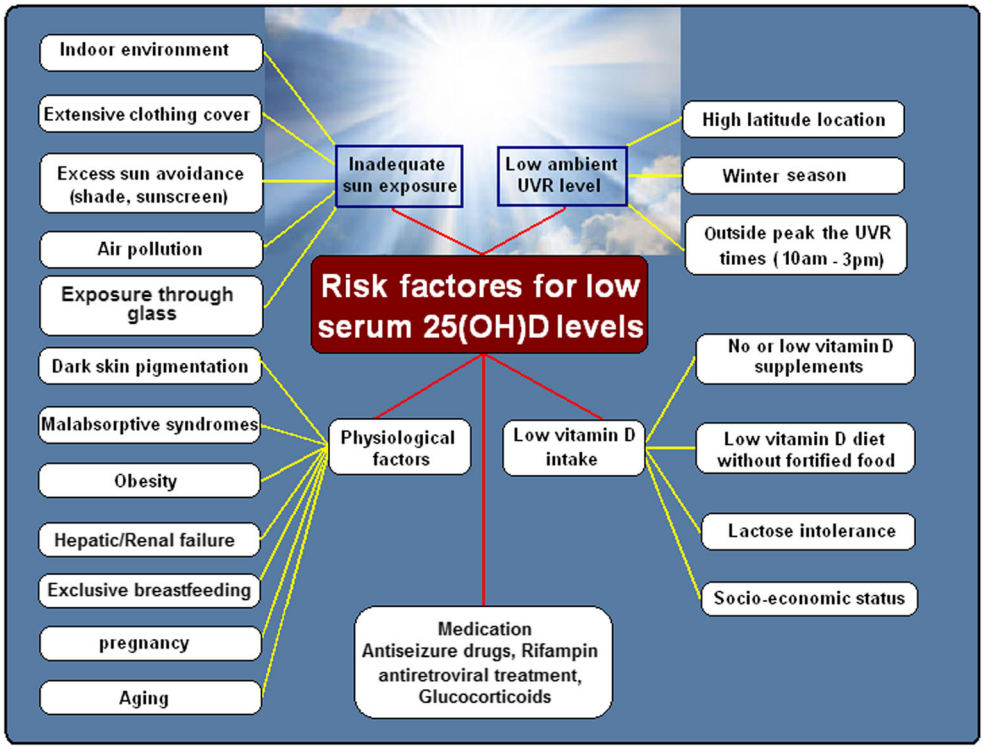


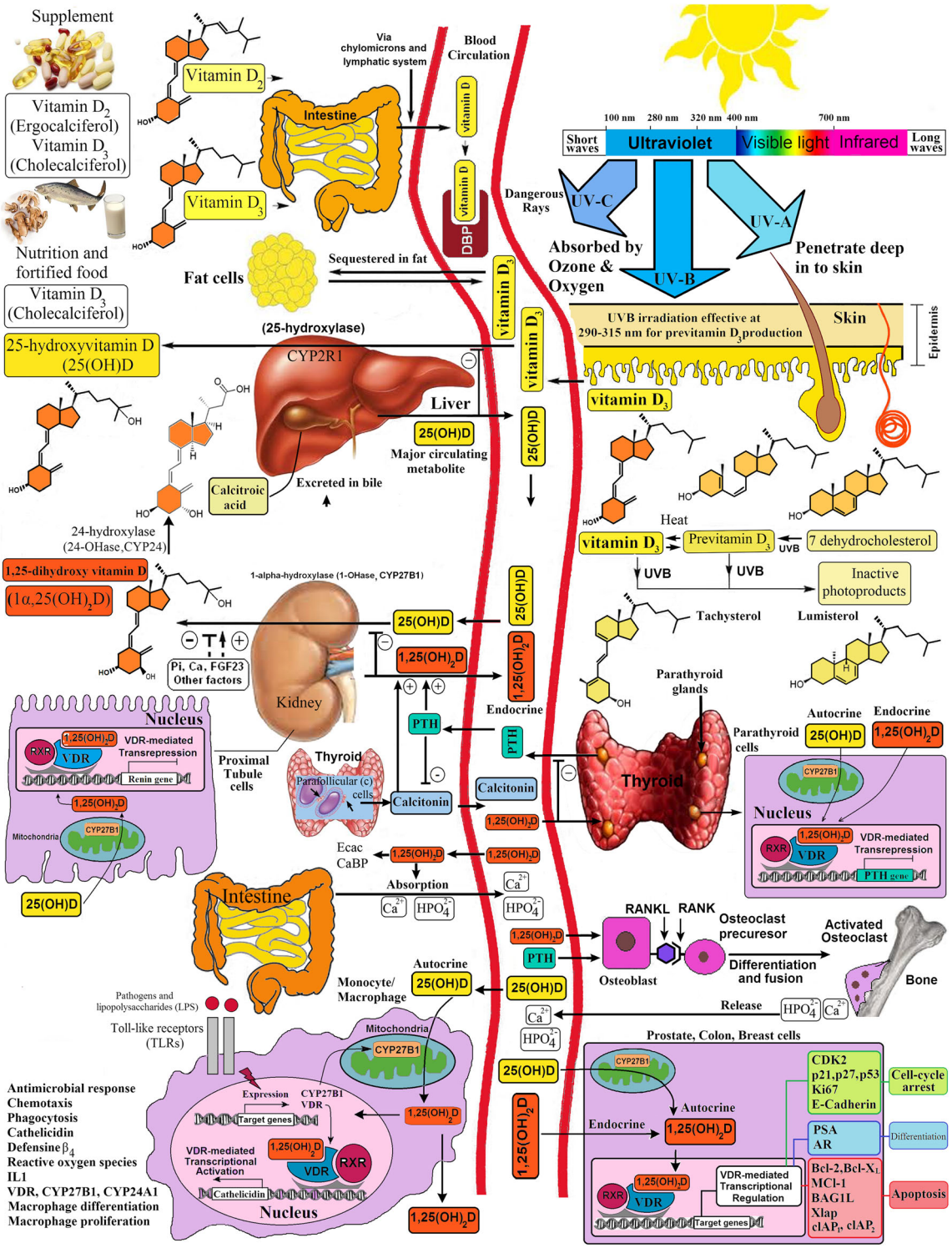
Fig. 4 Risk factors of low vitamin D status. (Holick copyright 2013, reproduced with permission)

converted to 25(OH)D. This metabolite then reenters the circulation and travels to the kidneys where is converted to the active form, 1,25-dihydroxyvitamin D [1, 25, 34] (Fig. 5).

It has been estimated at no more than 1% of the total solar UVB radiation ever reaches the earth's surface at the equator in the summer [34, 35, 38, 39]. There are several factors that influence how much solar UVB reaches the earth surface including first-order Rayleigh scattering by the atmosphere, attenuation by air, absorption by molecular oxygen and ozone, and the line structure in the solar spectrum [38–42]. The ozone in the atmosphere is very efficient in absorbing UVB radiation. When the zenith the angle of the sun becomes more oblique the path length increases resulting in ozone absorbing more of the UVB radiation thereby decreasing the amount reaching the earth surface [34, 38–42]. This is the explanation for why exposure to the sun above and below approximately 33° in the winter does not result in any significant production of vitamin D [34, 35, 43]. This also explains why very little if any vitamin D is produced in the skin during sun exposure before 9 AM and after 3 PM [34, 35, 39, 43]. Melanin and sunscreens both efficiently absorb UVB radiation thereby diminishing the effectiveness of the sun in producing vitamin D and the skin [34, 44]. A person with a skin type VI requires at least 5–10 times longer exposure compared to a person with skin type II [44]. The proper application of a sunscreen (2 mg/square centimeter) with a sun protection factor (SPF) of 30 absorbs 97.5% of the UVB radiation on the surface of the skin thereby decreasing production of vitamin D by 97.5% [34, 45]. Clothing and glass absorbs all UVB radiation and therefore prevents vitamin D production during sun exposure [34, 46, 47].

4 Treatment and prevention of vitamin D deficiency and insufficiency

There are 2 forms of vitamin D. Vitamin D_3 (cholecalciferol) is produced in the skin during sun exposure and is also present in oily fish and cod liver oil [1, 25, 34]. (Fig. 5) Vitamin D_3 in supplements is either derived from fish oil or produced from cholesterol that is obtained from lanolin in sheep's wool. Vitamin D_2 (ergocalciferol) was produced commercially from UV irradiated yeast. It is also present in mushrooms exposed to sunlight or ultraviolet B radiation and in sun-dried mushrooms [48]. Vitamin D_2 has been used for more than 50 years for the treatment and prevention of vitamin D deficiency [1, 25, 34]. It is also used to fortify some foods such as milk with vitamin D. However some reports raised the question as to whether vitamin D_2 was as effective as vitamin D_3 in maintaining blood levels of 25(OH)D [49–53]. One study reported that vitamin D_2 increased the destruction of vitamin D_3 suggesting that ingestion of vitamin D_2 increased risk for that patient becoming vitamin D deficient more quickly if vitamin D_2 was used [51]. This may be true when given as a single bolus dose but it is not true when given chronically. Several additional studies have appeared evaluating



physiologic doses (1000 IUs or 2000 IUs) of vitamin D_2 and vitamin D_3 on total blood levels of 25(OH)D [48, 54, 55]. These studies reported not only did ingesting 1000 IUs of vitamin D_2 raise blood levels of 25(OH)D to the same levels as those ingesting 1000 IUs of vitamin D_3 but that the 25(OH)D_3 did not significantly decline. Studies evaluating 50,000 IUs of vitamin D_2 every 2 weeks for the treatment and prevention of recurrent vitamin D deficiency for up to 6 years demonstrated it was effective in maintaining total 25(OH)D levels above 30 ng/mL [56]. To be certain that 25(OH)D_2 was converted in the kidneys to 1,25(OH)$_2D_2$ as efficiently as 25(OH)D_3 serum samples from the study where adults receive 1000 IUs of vitamin D_2 or vitamin D_3 were analyzed for 1,25(OH)$_2D_2$ and 1,25(OH)$_2D_3$. Remarkably,

◀ **Fig. 5** Schematic representation of the synthesis and metabolism of vitamin D for skeletal and non-skeletal function. During exposure to sunlight, 7-dehydrocholesterol in the skin is converted to previtamin D_3. Previtamin D_3 immediately converts by a heat-dependent process to vitamin D_3. Excessive exposure to sunlight degrades previtamin D_3 and vitamin 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(DBP), which transports it to the liver, where vitamin D is converted by the vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by 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 [$1,25(OH)_2D$]. $1,25(OH)_2D_3$ is then taken up by target cells and targeted to intracellular D-binding proteins (IDBP) to mitochondrial 24-hydroxylase or to the vitamin D receptor (VDR). The $1,25(OH)_2D_3$-VDR complex heterodimerizes with the retinoic acid receptor (RXR) and binds to specific sequences in the promoter regions of the target gene. The DNA bound heterodimer attracts components of the RNA polymerase II complex and nuclear transcription regulators. Serum phosphorus, calcium fibroblast growth factors (FGF-23), and other factors can either increase or decrease the renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. $1,25(OH)_2D$ increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize $1,25(OH)_2D$ to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. $1,25(OH)_2D$ enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel (ECaC) and the calbindin 9 K (calcium-binding protein, CaBP). $1,25(OH)_2D$ is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of the NF-kB ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL, which induces the preosteoclast to become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote the mineralization of the skeleton. Autocrine metabolism of 25(OH)D; when a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as Mycobacterium tuberculosis or its lipopolysaccharide, the signal up-regulates the expression of VDR and 1-OHase. A 25(OH)D level of 30 ng/ml or higher provides adequate substrate for 1-OHase to convert 25(OH)D to $1,25(OH)_2D$ in mitochondria. $1,25(OH)_2D$ travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as M. tuberculosis. It is also likely that the $1,25(OH)_2D$ produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. When the 25(OH)D level is approximately 30 ng/ml, the risk of many common cancers is reduced. It is believed that the local production of $1,25(OH)_2D$ in the breast, colon, prostate, and other tissues regulates a variety of genes that control proliferation, including p21 and p27, as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. Once $1,25(OH)_2D$ completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 24-OHase, which enhances the catabolism of $1,25(OH)_2D$ to the biologically inert calcitroic acid. Thus, locally produced (autocrine) $1,25(OH)_2D$ does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity, and the local production of 1,25(OH)2D inhibits the expression and synthesis of parathyroid hormone. The $1,25(OH)_2D$ produced in the kidney enters the circulation and can down-regulate renin production in the kidney and stimulate insulin secretion in the beta islet cells of the pancreas. (Holick copyright 2013, reproduced with permission)

as expected, when the kidney was provided $25(OH)D_2$ it converted it to $1,25(OH)_2D_2$. As a result of the increase in $1,25(OH)_2D_2$ the $1,25(OH)_2D_3$ decreased by the same amount so that the total $1,25(OH)_2D$ did not change from baseline [55]. This was expected since the blood level of $1,25(OH)_2D$ is tightly regulated by parathyroid hormone and other factors [1, 25].

In the United States only vitamin D_2 is available as a pharmaceutical because it predated the FDA and was grandfathered as a pharmaceutical. Vitamin D_3 was never evaluated as a pharmaceutical but is widely available as a supplement. The problem in the United States is that a pharmacy can obtain this supplement from several different manufacturers and we don't know the quality of the supplement whereas we do for the pharmaceutical vitamin D_2. With this said, vitamin D_3 supplements produced by respected national brands are perfectly fine. I have tested and demonstrated that there was an appropriate amount of vitamin D_3 as stated on the label in many well-respected national brands. For my patients who wish to take a vitamin D supplements, I recommend that they take a national brand of vitamin D_3. However if they are vegans I will recommend they take vitamin D_2.

It's been argued that most studies have used vitamin D_3 to demonstrate fracture efficacy and therefore why should we be using vitamin D_2 to treat our patients for vitamin D deficiency. Based on all the evidence there is no reason to suspect that vitamin D_2 would not have the same fracture benefit as vitamin D_3 because vitamin D_2 has the same biological functions on calcium metabolism as vitamin D_3. It is also been suggested that vitamin D_2 does not have any other health benefits such as decreasing risk for mortality and malignancies [57]. However these conclusions are mainly based on meta-analyses of studies that reported on vitamin D_2 intake but not on studies specifically comparing vitamin D_2 to vitamin D_3. Furthermore most of these studies did not report on blood levels of $25(OH)D_2$. Evidence does suggest that the half-life of $25(OH)D_2$ is shorter than $25(OH)D_3$. (58) This might suggest that vitamin D_2 is less effective than vitamin D_3 in its biologic actions. However one of the reasons why $25(OH)D_2$ has a shorter half-life is because it is not bound as tightly to DBP as $25(OH)D_3$ [58]. This suggests that there would be a higher free level of $25(OH)D_2$ compared to the free level of $25(OH)D_3$ and therefore theoretically since it is the free level that is thought to have the most physiologic benefit that it might be expected that vitamin D_2 would be more biologically effective than vitamin D_3. The observation by Chun et al. [58] supports this hypothesis. They evaluated the effect of dietary vitamin D_2 in comparison to dietary vitamin D_3 on free total levels of 25(OH)D in C56BL/6 mice and at 16 weeks evaluated by histomorphometry the effect of

these levels on bone morphology. The total 25(OH)D were essentially the same for the mice ingesting vitamin D_2 (33.3+ −4.4 ng/mL) compared to the mice receiving dietary vitamin D_3 (31.7+ −2.1 ng/mL) which is consistent with the clinical observations [54, 55, 58].The free 25(OH)D levels however were almost twice as high in the mice that received vitamin D_2 (17.4 pg/mL) compared to the mice that received vitamin D_3 (8.4 pg/mL) in their diets for 16 weeks. This translated into a positive benefit by the demonstration that the mice that received dietary vitamin D_2 had significantly higher bone volume/total volume and trabecular number compared to the mice receiving the same amount of dietary vitamin D_3. This study helps support the concept that vitamin D_2 supplementation is as effective, and may be even more effective, than vitamin D_3 supplementation at least regarding bone health. All of these observations in total would suggest that vitamin D_2 is at least if not more beneficial than supplemental vitamin D_3 and should put to rest the scientifically unfounded reluctance to use vitamin D_2 to treat and prevent vitamin D deficiency.

Because vitamin D_2 is a pharmaceutical and is only available in the form of 50,000 IUs in a capsule it was evaluated for the treatment and prevention of vitamin D deficiency in adults. 50,000 IUs of vitamin D_2 given once a week for 8 weeks is an effective strategy to treat vitamin D deficiency [3, 56]. It has been suggested that patients who have undetectable blood levels of 25(OH)D be treated with more vitamin D for a longer period of time. Although this may seem like good common sense, it turns out not to be true. The reason is that there are at least 4 different 25-hydroxylases in the liver some of which efficiently convert even a small amount of vitamin D rapidly to 25(OH)D. This is the explanation for why giving 600–800 IUs of vitamin D daily will rapidly raise blood levels of 25(OH)D into the range of 15–20 ng/mL [9, 59]. However once a person with normal body weight reaches approximately 20 ng/mL it now requires 100 IUs of vitamin D to raise blood levels of 25(OH)D by approximately 0.6–1 ng/mL [9, 54–56, 60]. This is also explanation for why giving 1000 IUs of vitamin D daily to an adult who has a blood level of approximately 18–20 ng/mL is not effective in raising blood levels of 25(OH)D above 30 ng/mL [54].

To prevent recurrent vitamin D deficiency it is important to recognize the reason for why the patient was found to be vitamin D deficient i.e. because he or she was not obtaining an adequate amount of vitamin D from either dietary or sunlight sources. To prevent recurrence, administering 50,000 IUs (1.25 mg) of vitamin D_2 once every 2 weeks is not only effective but also safe for at least 6 years [56, 61]. (Fig. 6) Alternative strategies is to treat vitamin D deficiency with 5000 IUs daily for 2 months followed by a maintenance dose of between 2000 and 3000 IUs of vitamin D_2 or vitamin D_3 daily. To achieve blood levels in the range of 40–60 ng/mL requires a daily dose of 4000–5000 IUs of vitamin D_2 or vitamin D_3 daily [60, 62]. Pregnant women who received 4000 IUs daily of vitamin D_3 throughout their pregnancy maintained a 25(OH)D level of approximately 50 ng/mL with no evidence for toxicity based on no change in their urinary and serum calcium levels [63].

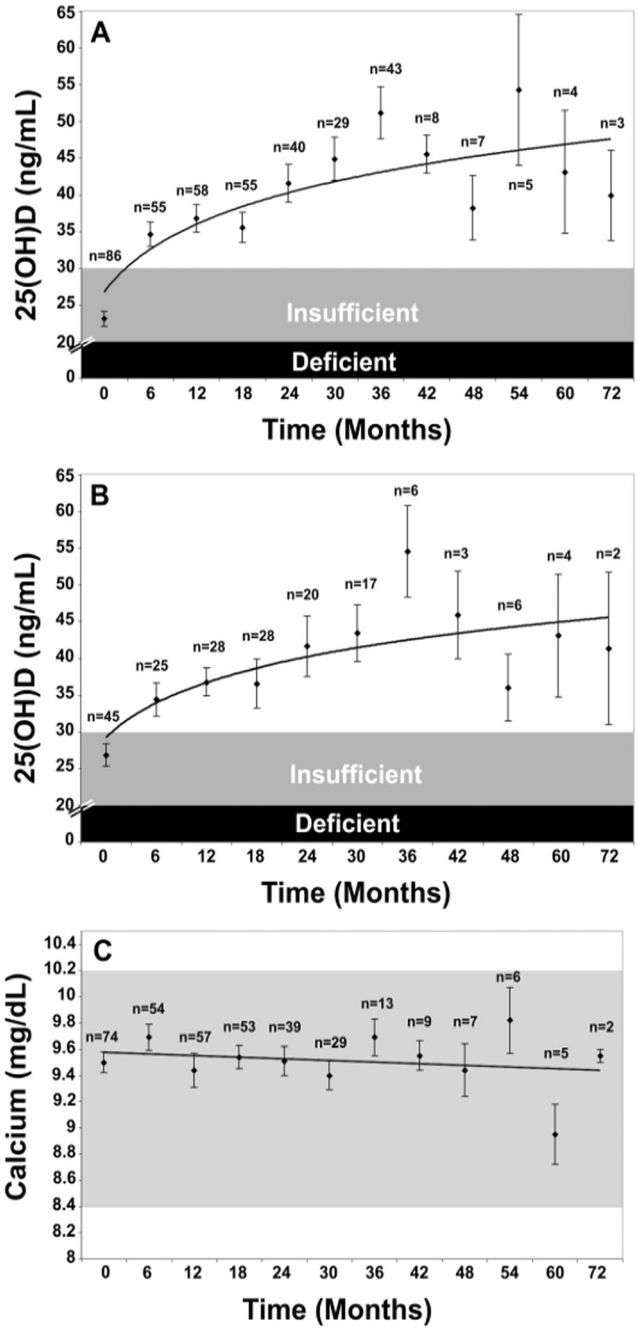
Obese adults with a BMI >30 require 2–3 times more of vitamin D to both treat and prevent vitamin D deficiency [9, 64, 65]. This is because vitamin D being fat soluble gets diluted in the body fat and is not bioavailable. Patients with inflammatory bowel disease and gastric bypass surgery are less efficient in absorbing the fat soluble vitamin D and often need higher doses to treat and prevent vitamin D deficiency. In some cases where vitamin D cannot be absorbed in the gastrointestinal tract exposure to sunlight or artificial sunlight i.e. a UVB lamp such as the Sperti lamp or a tanning bed that emits UVB radiation can be an effective alternative to treat and prevent deficiency [34, 35, 66–68].

Neonates should receive 400 IUs of vitamin D daily as soon after birth as possible especially for breast fed infants since human breast milk contains very little, if any, vitamin D unless the mother is ingesting approximately 6400 IUs of vitamin D daily [9, 69]. To quickly correct infantile vitamin D deficiency infants can receive 2000 IUs of vitamin D daily for 6–8 weeks [9, 70]. For infants where there is concern that they might not be seen again, the infants can receive Stoss therapy which is very high dose usually 250,000 IUs of vitamin D intramuscularly to prevent infantile rickets [71, 72]. Toddlers and children who are vitamin D deficient can be treated with 50,000 IUs of vitamin D once a week for 6 weeks or 2000 IUs of vitamin D daily without concern for toxicity [9, 70].

Some healthcare professionals who have available to them active vitamin D i.e. $1,25(OH)_2D_3$ (calcitriol) or its active analog 1-alpha-hydroxyvitamin D_3 believe that giving these analogs is an effective way to treat vitamin D deficiency. However these analogs not only have a relatively short half-life but can cause hypercalciuria and hypercalcemia and should not be used to treat vitamin D deficiency. These active forms of vitamin D however are effective in treating inborn and acquired disorders in the metabolism of 25(OH)D to $1,25(OH)_2D$ especially in patients with severe chronic kidney disease [1].

5 Vitamin D toxicity

Vitamin D intoxication is extremely rare. One cannot become vitamin D toxic from sun exposure because excess vitamin D is destroyed by the sun [34]. The only cause is due to nonintentional or intentional ingestion of excessively high quantities of vitamin D for a prolonged period of time. [73–76] Examples include a misunderstanding of the difference between micrograms and milligrams and a manufacturer putting in 1000 times more vitamin D than was on the label



◀ **Fig. 6** **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 5 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 two 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 ref. [56]

which was 1000 IUs in a capsule. The consumer of this product was advised to take 4 capsules a day for a total of 4000 IUs. However consumers were taking 4 million IUs daily for several months to more than a year [73]. A Canadian manufacturer did not dilute the crystalline vitamin D and the consumer who took 2 teaspoons a day believing that he was taking 2000 IUs daily had received more than 1 million IUs a day for more than a year [74]. A small dairy in Massachusetts inadvertently was adding up to 250,000 IUs of vitamin D in 8 oz of milk. Some of these consumers presented with overt vitamin D intoxication including a serum calcium as high as 16 mg/dL (normal range 8.6–10.6 mg/dL) and an elevated serum phosphate level in the range of 5–6 mg/dL (normal range 2.7–4.5 mg/dL). Their blood levels of 25(OH)D were in the range of 350–550 ng/dL [75].

6 Concerns about the J-curve and U-curve regarding blood levels of 25(OH)D

The IOM in its report raised concerns about raising blood levels of 25(OH)D above 50 ng/mL [7]. The IOM panel members agreed that vitamin D deficiency is associated with an increased risk for mortality especially from cardiovascular disease. The IOM panel members plotted a few studies reporting the relationship of mortality with blood levels of 25(OH)D. They showed a significant decline in mortality until the blood level of 25(OH)D approached 30 ng/mL and then showed a slight increase that was apparent at 50 ng/mL. The IOM panel members concluded that there should be concern about a potential increased risk for mortality if the blood level of 25(OH)D is above 50 ng/mL. This is known as J-curve or U-curve effect. However one of the studies that they plotted actually concluded that there continued to be at decreased risk for mortality from men above 50 ng/mL and that only in women there was a possibility of a slight increased risk for mortality [77]. Several publications have appeared challenging the concept of the so-called J-U-curve. [78, 79] First and foremost very few of these subjects in any of the studies had blood levels above 50 ng/mL. However more importantly the question that was never asked was how was it that some individuals in these studies had a blood level of 25(OH)D above 50 ng/mL. One possible explanation was that these

individuals were actually vitamin D deficient and being treated for vitamin D deficiency. To confirm this possibility Kroll et al. [79] reported on 3.8 million blood samples collected in the United States in adults over a two-year period of time. Because vitamin D_2 is routinely used the treat vitamin D deficiency the samples were analyzed by liquid chromatography tandem mass spectroscopy for the presence of 25(OH)D_2. Remarkably 57% of samples that had a total 25(OH)D of 50 ng/mL or greater had detectable levels of 25(OH)D_2. This suggested that these individuals were being treated for vitamin D deficiency and therefore would be more likely to be at higher risk for mortality due to their previous chronic vitamin D deficiency [79].

7 Conclusion

There continues to be contentious debate about what blood level of 25(OH)D is considered to be deficient and sufficient [7, 9, 10, 79–81]. It is in part based on the definition of vitamin D deficiency as to how much of vitamin D is required to be vitamin D sufficient. The IOM used a population model and determined that 400, 600 and 800 IUs daily is all that is required for neonates up to one year, children and adults up to 70 years and adults over 70 years respectively to achieve a 25(OH)D of 20 ng/mL in 97.5% of the population [7]. The IOM recommendations were not intended to provide guidance for the treatment and prevention of vitamin D deficiency. It was up to professional associations to make those recommendations. The Endocrine Society, National and International Osteoporosis Foundations and the American Geriatric Society chose to define vitamin D sufficiency as the blood level of 25(OH)D of at least 30 ng/mL [9, 12]. They also considered a blood level up to 100 ng/mL as perfectly safe. The Endocrine Society recommend a preferred range of 40–60 ng/mL. This is the range that likely our hunter gatherer forefathers achieved while being exposed to sunlight on a daily basis. The body has a huge capacity to produce vitamin D. Exposure of half an adult body to about 50% of the amount of sunlight that would cause a mild sunburn 24 h later is equivalent to ingesting approximately 5000 IUs of vitamin D daily [34, 35]. This is consistent with the observation made in Maasai herders who maintained blood levels of 25(OH)D of 40–50 ng/mL [82]. To achieve and maintain this level would require an adult to ingest 4000–5000 IUs daily of vitamin D [60, 62]. Therefore the recommendations for vitamin D intake of 400–1000 IUs, 600–1000 IUs and 1500–2000 IUs daily for children under one year, children 1–18 years and all adults respectively to treat and prevent vitamin D deficiency by the Endocrine Society is reasonable [9]. Teenagers however should be treated as adults and should also be receiving at least 1500–2000 IUs a day [83]. The IOM recommended the upper limit for most children and adults be at 4000 IUs daily. The Endocrine Society agreed that 4000 IUs daily is reasonable as the upper limit for children but for adults 10,000 IUs daily is more reasonable especially since obese people require 2–3 times more vitamin D to treat and prevent recurrent vitamin D deficiency [9, 62].

There are a multitude of studies relating the health benefits of vitamin D and sun exposure for reducing risk for many chronic illnesses including deadly cancers, autoimmune diseases including multiple sclerosis, rheumatoid arthritis, Crohn's disease in type 1 diabetes, cardiovascular disease, neurocognitive dysfunction, type 2 diabetes and infectious diseases. [1, 25, 34, 35, 84, 85].

The abstinence message of avoiding all direct sun exposure without sun protection by many dermatology societies [86] has not resulted in a significant decline in the incidence of the most deadly form of skin cancer, melanoma [87]. This is expected since most melanomas occur on the least sun exposed areas and occupational sun exposure decrease decreases the risk for melanoma [88, 89]. Furthermore obesity has been linked to an increased risk for both melanoma and nonmelanoma skin cancer [87]. Excessive sun burning increases risk not only for the deadly melanoma but also for non-melanoma skin cancer [88, 89]. Felton et al. [90] reported that people with skin type II living in the UK and exposed to UV radiation that would be expected to be received in the summer, did as expected, have increased DNA damage in the epidermis. This exposure also significantly increased their blood level of 25(OH)D. At the end of the study an evaluation of the epidermis revealed a marked decline in DNA damage that was reflected by a decrease in urinary DNA metabolites. This demonstrated that the Caucasian skin type II that evolved as people migrated north and south of the equator not only permitted a more efficient production of vitamin D but at the same time developed mechanisms to overcome the DNA damage that was associated with being exposed to the vitamin D-UVB solar radiation [91]. Recently the World Health Organization has recognized on its website that sensible sunlight does provide health benefits including the production of vitamin D. However it is hard to define sensible sun exposure since time of day, season, latitude, altitude and skin pigmentation all can dramatically influence how much vitamin D is produced in the skin when exposed to sunlight [34, 35]. As a result an app dminder.info which is free for the android and apple formats has been developed to provide a user with information as to when and how much vitamin D can be produced during sun exposure anywhere on the planet anytime of the year for all skin types [91]. It also advises a user when they've been exposed to enough sunlight and to seek sun protection so that they do not acquire a sunburn.

With all of the mounting evidence for a wide variety of health benefits associated with vitamin D sufficiency there is no downside to be improving everyone's vitamin D status. The goal should be to have a blood level of 25(OH)D of at

least 30 ng/mL; the preferred range being 40–60 ng/mL. This can be achieved by increasing everyone's vitamin D supplementation to the levels recommended by the Endocrine Society [9] as well as obtaining sensible sun exposure [34, 90–94]. There is no need to be screening every one for the vitamin D status [7, 9]. It is much more cost effective to increase food fortification with vitamin D [34, 90–93, 95, 96] and encourage vitamin D supplementation and sensible sun exposure. However those individuals with fat malabsorption syndromes, those who had had gastric bypass surgery or have other risk factors or inborn or acquired disorders in vitamin D metabolism do require screening with followup measurements of 25(OH)D [1, 9, 62].

Compliance with ethical standards This is a review and therefore there are no issues regarding compliance and ethical standards.

Conflict of interest The author declares that he is a consultant for Quest Diagnostics, Ontometrics Inc. and is on speaker's Bureau for Sanofi Inc.

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