

# A Dermatologist's Perspective on Vitamin D

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## Abstract

Vitamin D is a fat-soluble steroid hormone that is crucial for human health and has recently generated controversy regarding its role in human health and disease. In this Special Article, we discuss our dermatologic perspective on vitamin D in a question-and-answer format. We discuss methods of obtaining vitamin D, including cutaneous photobiosynthesis, diet, and supplements and include the recent US Institute of Medicine recommendations. Other reviewed topics include the associations among skin pigmentation, climate, photoprotection, and vitamin D levels. We also elaborate on the popular interest in sun exposure as a method of normalizing vitamin D levels in the context of the risks of solar and artificial radiation. We also discuss groups at risk for vitamin D inadequacy, the need for testing serum vitamin D levels, and the role of phototherapy in patients with malabsorption conditions and hypervitaminosis D, with a focus on patients with sarcoidosis. Finally, we summarize our recommendations on vitamin D.

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Vitamin D is a fat-soluble steroid hormone that is obtained by photoexposure, diet, or supplements and is crucial for human health. It is globally known for its importance in bone mineral metabolic health promotion and was traditionally known as the “sunshine” vitamin because of its antirachitic properties. In recent years, vitamin D has been studied for its potential role in the prevention of cancers, cardiovascular diseases, autoimmune diseases, and other chronic conditions.<sup>1-9</sup>

Vitamin D has both endocrine and autocrine functions. The endocrine effects of vitamin D are involved in serum calcium homeostasis. The autocrine effects of vitamin D depend on genetic transcription unique to the type of cell expressing nuclear vitamin D receptors. These potential effects include inhibition of cell proliferation, promotion of cell differentiation, and apoptosis. These functions may in turn have roles in cancers, immunity, and many organ systems.<sup>1-9</sup> The potential myriad effects of this vitamin in human health and disease have led to popular interest in vitamin D inadequacy and the best method to normalize suboptimal levels. To date, however, no definitive data on causal relationships are available for the role of vitamin D in areas other than calcium homeostasis and bone health.<sup>10</sup> In this article, we address frequently asked questions about vitamin D from a dermatologist's perspective, using the best available evidence to date.

## HOW DO WE OBTAIN VITAMIN D?

There are only 3 sources of vitamin D: sunlight, diet, and vitamin D supplements.<sup>1-9</sup>

### Sunlight

The most well-known source of vitamin D is sun exposure (Figure 1). Vitamin D is a fat-soluble pro-hormone steroid. On exposure to the UV-B portion

of sunlight at a mean  $\pm$  SD of  $300 \pm 5$  nm, the precursor 7-dehydrocholesterol in the plasma membrane of both keratinocytes and fibroblasts is converted to previtamin D<sub>3</sub>, the former in the basal and suprabasal layers of the epidermis of the skin (Figure 2). Previtamin D<sub>3</sub> is then converted to vitamin D<sub>3</sub> by a thermal, nonenzymatic process in the plasma membrane. Vitamin D<sub>3</sub> is then transported to the bloodstream.<sup>1-9,11,12</sup>

The UV-B action spectrum of vitamin D biosynthesis is the same as that responsible for the sunburn response and photocarcinogenesis. The conversion of previtamin D<sub>3</sub> to the inactive photoproducts lumisterol and tachysterol balances the cutaneous biosynthesis of vitamin D<sub>3</sub> as a feedback loop. This mechanism ensures that one cannot “overdose” on vitamin D<sub>3</sub> by photoexposure alone. After less than 1 minimal erythema dose (MED; ie, the amount of photoexposure required to produce faint pinkness in the skin at 24 hours after exposure), the concentration of previtamin D<sub>3</sub> reaches maximal levels and further UV radiation merely results in the production of inactive metabolites.

Cutaneously synthesized vitamin D<sub>3</sub> is bound to vitamin D-binding protein (VBP), whereas dietary vitamin D<sub>2</sub> and vitamin D<sub>3</sub> are bound to both VBP and lipoproteins. Both vitamin D<sub>2</sub> and D<sub>3</sub> are hydroxylated by 25-hydroxylase in the liver to form 25-hydroxyvitamin D (25[OH]D).<sup>1-9,11,12</sup>

25-hydroxyvitamin D is the major circulating form of vitamin D, and its serum levels are widely used as a reflection of total body stores of vitamin D. It is biologically inactive, however, and requires hydroxylation in the kidney to form the biologically active 1,25-dihydroxyvitamin D (1,25[OH<sub>2</sub>]D) (Figure 1).<sup>1-9,11,12</sup> Megalin and cubilin are endocytic receptors in the proximal tubule cells of the kidney. They are involved in reabsorption of VBP, which, in the presence of 1- $\alpha$  hydroxylase, results in intracellular

conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D.<sup>13,14</sup> 1,25-dihydroxyvitamin D regulates calcium metabolism in an endocrine manner by enhancing intestinal calcium absorption, reducing renal excretion of calcium by its effects on parathyroid hormone (PTH), and mobilizing calcium from the skeleton through resorption.<sup>1-9,11,12</sup>

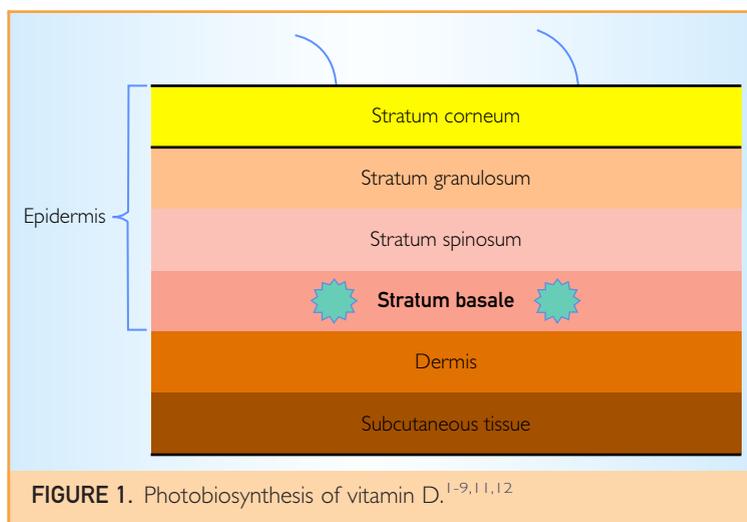
In vitro studies show that 25-hydroxylase, but not 1- $\alpha$  hydroxylase, is present in dermal fibroblasts. There are extrarenal cells and organs that possess 1- $\alpha$  hydroxylase, including lung, breast, colon, prostate, keratinocytes, and monocytes. Human keratinocytes have demonstrated both an in vivo and in vitro autonomous capacity for vitamin D<sub>3</sub> metabolism and catabolism. 1,25-dihydroxyvitamin D formed by extrarenal organs acts in an autocrine manner. 1,25-dihydroxyvitamin D levels are tightly regulated and are relatively constant, whereas serum 25(OH)D levels vary widely over time in healthy individuals.<sup>1-9,11,12</sup>

Autocrine-acting 1,25(OH)<sub>2</sub>D acts as a steroid hormone and links a steroid hormone receptor to a vitamin D receptor. This complex then binds to a retinoic acid X receptor, which then binds to vitamin D response elements in the genome and subsequently modifies gene transcription. At least 60 human cell types express the vitamin D receptor, with an estimated 200 genes that are responsive to vitamin D. These genes are involved in processes such as cell proliferation, differentiation, apoptosis, and production of bactericidal proteins.<sup>1-9,11,12</sup>

Interestingly, there are also noncalcemic analogues of vitamin D that have been shown to have prodifferentiation and apoptotic effects. A recent study demonstrated that 20-hydroxyvitamin D<sub>2</sub> inhibited DNA synthesis in epidermal keratinocytes and melanoma cells; these effects were facilitated by interactions with the vitamin D receptor.<sup>15</sup> Furthermore, although the products of vitamin D<sub>3</sub> metabolism and 7-dehydrocholesterol metabolism, such as 1- $\alpha$  20-dihydroxyvitamin D<sub>3</sub>, 20-hydroxyvitamin D<sub>3</sub>, and 7-dehydropregnenolone, have little to moderate calcemic activity when compared with 1,25(OH)<sub>2</sub>D, they have been shown to have antiproliferative and prodifferentiation effects on human and mouse leukemia cells.<sup>16,17</sup>

### Dietary Sources

There are only a few natural sources of vitamin D. These sources include cod liver oil, cheese, egg yolks, mackerel, salmon, tuna fish, and beef liver (Table 1).<sup>3,9,18</sup> Because it is not easy for many individuals to obtain adequate vitamin D intake from natural dietary sources alone, many countries, including the United States, fortify foods such as orange juice, milk, yogurt, and cereal with vitamin D. For the past few years, vitamin D<sub>3</sub> has



been the most common type of vitamin D used for fortification.<sup>3,9,18</sup>

### Vitamin D Supplements

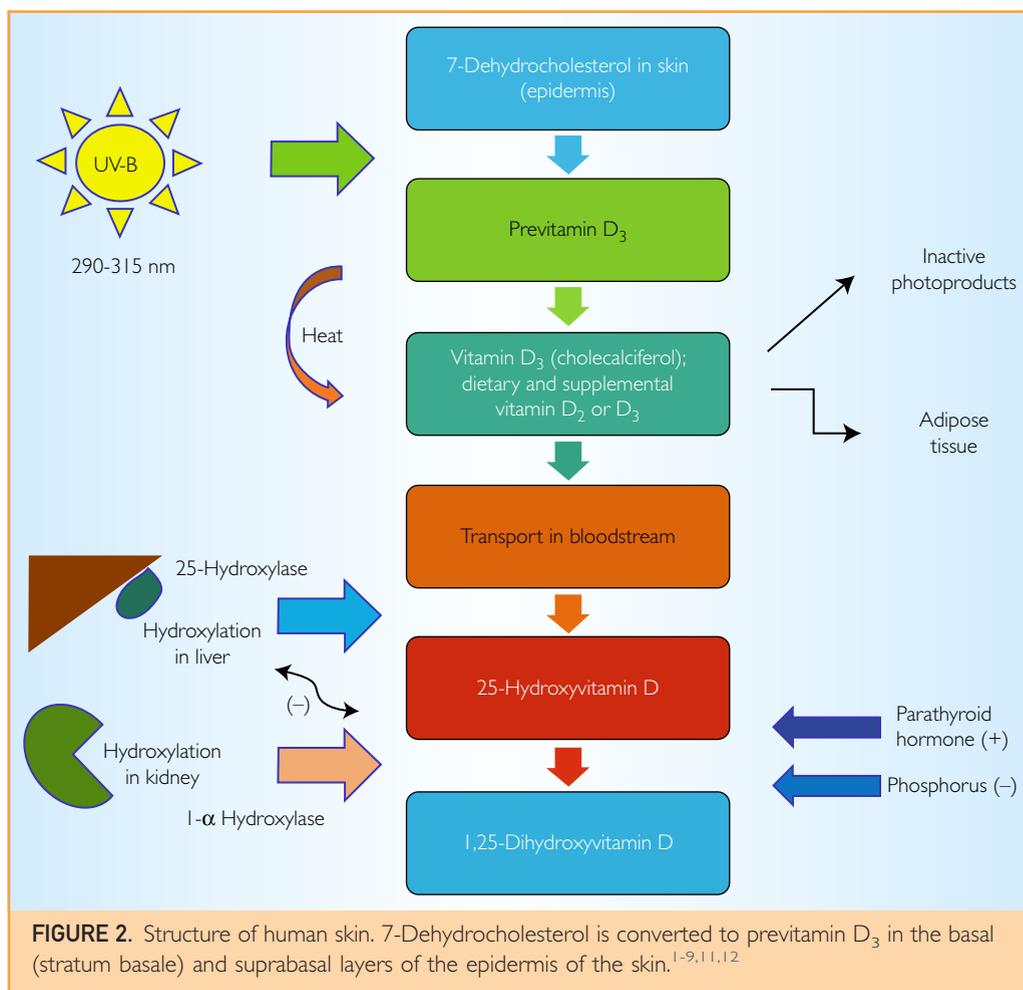
Many inexpensive supplemental vitamin D forms are readily available over the counter in both vitamin D<sub>3</sub> and vitamin D<sub>2</sub> forms and with or without calcium.

### ARE THERE DIFFERENCES BETWEEN VITAMIN D<sub>2</sub> AND D<sub>3</sub>?

There are 2 forms of vitamin D: vitamin D<sub>2</sub> and vitamin D<sub>3</sub>. Vitamin D<sub>2</sub> is naturally found in sun-dried mushrooms, such as shiitake mushrooms, and is also formed from UV irradiation of the yeast sterol ergosterol. Vitamin D<sub>3</sub> is synthesized in human skin and is present in vitamin D-rich food (Table 1).<sup>3,9,18</sup> The biological activity of vitamin D<sub>2</sub> vs vitamin D<sub>3</sub> is likely equivalent but is an active and controversial area of research.<sup>1,19-25</sup> Most vitamin D-fortified foods, vitamin D supplements, and multivitamins in the United States contain vitamin D<sub>3</sub>. The prescription form of vitamin D in the United States, however, is vitamin D<sub>2</sub> (eg, as 50,000-IU capsules).<sup>1,3,9,18-25</sup>

### WHAT IS THE EVIDENCE THAT VITAMIN D HAS AN EFFECT ON HEALTH AND DISEASE?

This topic has been extensively reviewed elsewhere.<sup>3,26-28</sup> The relative strength of evidence for the effect of vitamin D on various diseases, which we have rated subjectively, is listed in Table 2.<sup>3</sup> Suffice it to state that in the recent report from the Institute of Medicine (IOM), it was concluded that the strongest evidence was only for the beneficial effect of



vitamin D on skeletal health, whereas evidence for the effect of vitamin D on extraskeletal outcomes was considered “inconsistent, inconclusive, and insufficient to inform nutritional requirements.”<sup>10</sup>

### DOES SKIN PIGMENTATION AFFECT VITAMIN D LEVELS?

Variation in skin color is an immediately noticeable human polymorphism. The causes of human skin pigmentation have been discussed from the time of Hippocrates in the fifth century. Aristotle and his followers developed a “climatic theory,” which related human features to their surroundings, including the association of darker skin pigmentation with warm environments.<sup>29</sup>

Differences in human skin pigmentation are due to varying epidermal melanin contents. Because epidermal melanin is a large polymer that absorbs photons across the entire visible light and UV range, its content determines the number of photons that can eventually result in the cutaneous synthesis of vitamin D<sub>3</sub>. There are 2 levels of natural selection

hypothesized to play a role in human skin pigmentation. The first is the need for photoprotection against high levels of equatorial UV-A and UV-B, which resulted in darker skin pigmentation. The second is to promote seasonal UV-B photosynthesis of vitamin D<sub>3</sub> in areas proximal to the poles, resulting in lighter skin pigmentation.<sup>1-8,29,32</sup> Vitamin D may even have a role in melanogenesis because melanocytes in situ express the vitamin D receptor.<sup>32</sup>

A study published in 1991 investigated the relationship between skin pigmentation and vitamin D<sub>3</sub> formation.<sup>31</sup> The investigators found that after a fixed dose of UV-B radiation, serum vitamin D<sub>3</sub> levels were significantly higher in white and Asian groups than in African American and East Indian groups. Interestingly, they also found that serum 1,25(OH)<sub>2</sub>D levels and VBP levels were similar in all groups, regardless of skin pigmentation.<sup>31</sup>

A study in 2004 detailed the 25(OH)D levels in different groups in the United States. White individuals had a mean serum level of 32 ng/mL (to convert

TABLE 1. Vitamin D and Dietary Intake

Food	Vitamin D, IU per serving
1 Tbsp of cod liver oil	1360
Sockeye salmon, cooked, 3 oz	447
Mackerel, cooked, 3 oz	388
Tuna fish, canned in water, drained, 3 oz	154
Orange juice, vitamin D fortified, 1 c	137 (amount varies by product)
Milk, vitamin D fortified, 1 c (nonfat, reduced fat, and whole)	115-124
Yogurt, fortified with 20% of the daily value for vitamin D, 6 oz	88
Beef liver, cooked, 3.5 oz	49
Ready-to-eat cereal, 10% of the daily value of vitamin D, ¾-1 c	40 (amount varies by product)
Egg, 1 large (vitamin D is in yolk)	41
Swiss cheese, 1 oz	6

Data from the National Institutes of Health Office of Dietary Supplements.<sup>18</sup>

to nmol/L, multiply by 2.496), Mexican Americans had a level of 24 ng/mL, and African Americans had a level of 20 ng/mL.<sup>33</sup> Furthermore, among individuals older than 60 years, more than 67% of whites and 88% of African Americans had serum levels lower than 32 ng/mL.<sup>33</sup> A study published in 2010 evaluated the seasonal variations of vitamin D levels at high latitudes in fall vs winter with consideration of other factors, including skin pigmentation, sun exposure, and dietary vitamin D intake. They reported that South Asians and East Asians had substantially lower 25(OH)D levels than Europeans.<sup>34</sup> Another 2010 study assessed the association among skin pigmentation, sun exposure, skin reflectance, vitamin D intake, and body surface area exposed to the sun.<sup>35</sup> The authors concluded that to maintain serum 25(OH)D levels of greater than 30 ng/mL, individuals of European ancestry with high sun exposure need a supplemental dietary intake of 1300 IU/d of vitamin D, whereas individuals of African ancestry with low sun exposure need 2100 to 3100 IU/d year round.<sup>35</sup>

A recent study demonstrated that after broadband UV-B (290-320 nm) exposure in a laboratory setting, the increase in serum 25(OH)D levels was independent of the constitutive skin pigmentation of the studied individuals.<sup>36</sup> This finding suggests that the innate vitamin D biosynthesis abilities of the skin of individuals of different pigmentation are similar. This study was performed during the winter season in Denmark, when melanin content was lower and expected to reside in the deeper basal layer of the epidermis, therefore playing a relatively less protective role.<sup>36</sup> In summary, most available evidence indicates that there is an inverse association between skin pigmentation and serum 25(OH)D levels.<sup>1-8,29-36</sup>

#### DO PEOPLE RESIDING IN AREAS WITH SUNNY CLIMATES HAVE ADEQUATE SERUM VITAMIN D LEVELS?

Authors of a study published in 2007 recruited 93 healthy, young, clinically tanned adults from the University of Hawaii and a Honolulu skateboard shop.<sup>37</sup> These individuals had a mean of 29 hours of sun exposure per week during the 3 months preceding the study, and 40% of them reported never using sunscreen. The group's mean 25(OH)D concentration was 32 ng/mL, and 51% of the study's participants had serum 25(OH)D levels below 30 ng/mL, levels considered inadequate at the time of the study.<sup>37</sup>

Similarly, studies from Santiago (Chile), Kashmir (India), and East Asia reported that more than 50% of individuals living in areas with sunny climates had inadequate serum vitamin D levels (<30 ng/mL).<sup>38-41</sup> Possible explanations for these findings include photoprotection practices (due to lifestyles or cultural beliefs), older age and obesity (which are associated with lower serum 25(OH)D levels), and inadequate dietary intake.<sup>1-9,42</sup>

A 2010 review of published serum 25(OH)D levels in the northern hemisphere, however, reported mean levels in the winter of 48.3 nmol/L (ranging from a low of 29.0 nmol/L in Helsinki to a high of 62.3 nmol/L in Miami) and in the summer of 70.0 nmol/L (ranging from a low of 57.0 nmol/L in Kalamazoo to a high of 85.4 nmol/L in Boston).<sup>43</sup> Considering the November 2010 IOM recommendation that adequate levels of 25(OH)D are 50 nmol/L or higher,<sup>10</sup> this report strongly indicates that in the northern hemisphere inadequate vitamin D status in a population was most likely to occur only in those residing in high latitudes in the winter.<sup>43</sup>

**TABLE 2. Vitamin D and Human Diseases**

Disease	Evidence <sup>a</sup>
Skeletal health	+++
Cancer	+
Multiple sclerosis	+
Macular degeneration	+
Atopic dermatitis	+
Melanoma	+
Hypertension	+/-
Colorectal cancer	+/-
Cardiovascular disease	-
Diabetes mellitus type 2	-
Rarer cancers <sup>b</sup>	-
Depression	-

<sup>a</sup>Evidence is rated by the authors from strongest (+++) to no beneficial association (-).

<sup>b</sup>Rarer cancers are endometrial, esophageal, gastric, kidney, ovarian, and pancreatic cancers, and non-Hodgkin lymphoma.<sup>3</sup>

### WHAT SHOULD WE ADVISE PATIENTS ON PHOTOPROTECTION PRACTICES AND VITAMIN D LEVELS?

In laboratory settings, it has been shown that adequate application of a sunscreen with a sun protection factor (SPF) of 8 significantly suppressed the increase in 25(OH)D after one MED of simulated sunlight.<sup>44</sup> A review of available evidence published in 2009, however, concluded that although sunscreens can reduce significantly the cutaneous synthesis of vitamin D under very strictly controlled conditions, their normal use by the general population does not generally result in vitamin D insufficiency.<sup>45</sup> A possible explanation for this conclusion is the well-documented fact that in actual use most individuals apply sunscreens at much lower concentrations than the concentration mandated for sunscreen SPF testing (0.5-0.8 mg/cm<sup>2</sup> in actual use vs 2 mg/cm<sup>2</sup> required for SPF determination), hence resulting in a significantly lower in-use SPF compared with the labeled SPF.<sup>46-48</sup>

It has been shown that full body exposure of fair-skinned individuals to 10 to 15 minutes of mid-day summer sun is equivalent to one MED and resulted in the synthesis of approximately 15,000 IU/d of vitamin D<sub>3</sub>.<sup>48</sup> By this reasoning, exposure of 15% of the body surface area (eg, face, hands, and arms) to a level of one-third MED should result in cutaneous biosynthesis of 1000 IU/d of vitamin D<sub>3</sub>.<sup>11,12,27,44,48-51</sup> It is difficult and not prudent to extrapolate these results to the general populace because cutaneous biosynthesis of vitamin D depends on factors that alter solar UV-B intensity, such as latitude, altitude, cloud cover, smog levels, and sea-

son. Other factors associated with vitamin D biosynthesis include body surface area exposed and skin pigmentation.<sup>1-9,11,12,48-50</sup>

The UV-B range responsible for cutaneous vitamin D synthesis is known to be carcinogenic. In fact, the International Agency for Research on Cancer, a World Health Organization agency, classified solar radiation as "carcinogenic to humans."<sup>52</sup> Many national organizations, including the American Academy of Dermatology and the National Council on Skin Cancer Prevention, have recommended that photoprotection be practiced.<sup>53-55</sup> Because vitamin D supplements can be obtained easily and inexpensively as over-the-counter preparations, for those concerned with or at risk for inadequate vitamin D status, vitamin D supplements should be taken.

### WHAT IS THE RELATIONSHIP BETWEEN THE USE OF TANNING BEDS AND VITAMIN D LEVELS?

Indoor tanning is a burgeoning and increasingly popular industry that has become more accessible to the general public during the last 30 years. Some estimates in recent years state that the indoor tanning business earns \$5 billion per year, with more than 28 million customers annually and more than 50,000 tanning facilities in the United States. The major emission spectra of tanning lamps is in the UV-A range (320-400 nm, which causes tanning) rather than in the UV-B range, the action spectrum of vitamin D biosynthesis.<sup>56</sup>

Although the use of tanning booths can cause increases in serum 25(OH)D levels, this may be confounded by higher overall duration of sun exposure in users.<sup>56</sup> In recent years, strong evidence has indicated that the use of tanning beds is addictive and associated with the development of skin cancers, including melanoma.<sup>52,56-64</sup> As previously mentioned, in 2007, the International Agency for Research on Cancer published a special report on human carcinogens and raised the classification of UV-emitting tanning devices to group 1 (carcinogenic to humans).<sup>52</sup> The World Health Organization has recommended a complete ban on indoor tanning for minors younger than 18 years.<sup>52</sup> On the basis of this evidence, there is no indication for the use of tanning beds to obtain adequate vitamin D status.

### WHAT ARE THE CURRENT RECOMMENDATIONS ON VITAMIN D INTAKE AND SERUM LEVELS?

In November 2010, after a 2-year study, the IOM released its recommendations on vitamin D.<sup>10</sup> The recommendations were made based on data on skeletal health only; data on extraskelatal outcomes, including cancer, cardiovascular diseases, diabetes

mellitus, and autoimmune disorders, were considered “inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements.”<sup>10</sup> In recognition of the wide variability of vitamin D synthesis secondary to sun exposure (due to factors such as cloud cover, season, time of day, and skin pigmentation) and the risks of skin cancer, the recommendations were made with an assumption of minimal or no sun exposure.<sup>1-12,57-64</sup>

In November 2010, the IOM established recommended dietary allowances (RDAs) for adults and allowable intake (AI) levels for infants (0-12 months of age) for vitamin D; RDA is defined as intake that meets the needs of 97.5% or more of the population, and AI is defined as a level of intake assumed to ensure adequate nutrition when there is lack of evidence to set an RDA.<sup>10,18</sup> The AIs and RDAs are as follow: 0 to 12 months of age, 400 IU/d; between 1 and 70 years of age, 600 IU/d; and older than 70 years, 800 IU/d. The RDA for pregnant and lactating women was also set at 600 IU/d. Furthermore, the IOM stated that serum 25(OH)D levels of 20 ng/mL cover the requirements for 97.5% of the population. The IOM also commented that although there are sparse data on upper serum levels of 25(OH)D, levels higher than 50 ng/mL “should raise concerns among clinicians about potential adverse effects.”<sup>10</sup> Upper intake levels (the highest daily intake likely to pose no risk) were as follows: for 1 to 3 years of age, 2500 IU/d; for 4 to 8 years of age, 3000 IU/d; and for 9 years and older, 4000 IU/d.<sup>10</sup>

### SHOULD TESTING FOR SERUM VITAMIN D LEVELS BE RECOMMENDED FOR ALL INDIVIDUALS?

In the United States, the cost of a serum 25(OH)D test is approximately \$100. Therefore, if testing were performed on all individuals, there would be an added economic burden to society.<sup>3,26</sup> As stated earlier, a recent review of serum 25(OH)D levels in individuals residing in the northern hemisphere showed adequate levels of greater than 20 ng/mL, with the exception of some regions in colder climates during the winter.<sup>43,49</sup> Therefore, we recommend testing for serum 25(OH)D levels in the appropriate clinical context only in individuals known to be at risk for vitamin D inadequacy (Table 3). Those at risk for vitamin D inadequacy include elderly individuals (>70 years old) because aged skin has decreased capacity to synthesize vitamin D, individuals with limited sun exposure, obese individuals, those with darker skin (Fitzpatrick skin phototypes IV-VI), and individuals with malabsorption syndromes because vitamin D is a fat-soluble vitamin.<sup>1-9,42,51,65-71</sup> Finally, because human breast milk contains only 25 IU/L of vitamin D in contrast to vitamin D-enriched infant formula (100 IU of

vitamin D<sub>3</sub> per 8 oz), vitamin D drop supplementation should be given to breastfed infants.<sup>1-9,67-69</sup>

### SHOULD UV-B PHOTOTHERAPY BE ADMINISTERED TO PATIENTS WITH MALABSORPTION DISORDERS TO ACHIEVE ADEQUATE VITAMIN D STATUS?

Most vitamin D is absorbed in the distal duodenum and proximal jejunum; therefore, patients with malabsorption disorders are at risk for inadequate vitamin D status.<sup>1-9,51,65,66</sup> It is well established that narrowband UV-B (311-313 nm) phototherapy results in increases in serum 25(OH)D levels.<sup>72-74</sup> Narrowband UV-B units are widely available in dermatology centers and offices and are also available as home units with a physician's prescription.<sup>73-75</sup>

A study published in 2008 that evaluated more than 4600 patients who received narrowband UV-B phototherapy from 1985 to 2002 found no increase in skin cancer development.<sup>75</sup> The cost of phototherapy in the United States is approximately \$50 per treatment, whereas the cost of a home unit is approximately \$2500. At this time, there are no data on the safety and efficacy of long-term, potentially lifelong phototherapy in patients with malabsorption issues. This is the reason that we recommend referring these patients to our endocrinology colleagues for management with careful monitoring of serum 25(OH)D levels.<sup>3,26,72-74</sup> The recent Endocrine Society Practice Guidelines on vitamin D recommended at least 6000 to 10,000 IU/d of vitamin D for patients with malabsorption disorders until a serum 25(OH)D level of 30 ng/mL is reached, with maintenance dosing of 3000 to 6000 IU/d.<sup>9</sup>

### SHOULD WE BE CONCERNED ABOUT HYPERVITAMINOSIS D?

In healthy adult patients, vitamin D has a good safety profile. Although the 2011 IOM recommen-

**TABLE 3. Individuals at Risk for Vitamin D Deficiency**

Individuals with low sun exposure (due to geography, photoprotection practices, or clothing worn because of cultural beliefs)
Exclusively breastfed infants
Elderly individuals, especially those with a history of or risk for falls and fractures
Obese individuals
Individuals with darker skin types
Patients with malabsorption conditions, such as inflammatory bowel disease
Patients with cystic fibrosis
Patients taking anticonvulsant and antifungal (eg, ketoconazole) medications
Patients taking medications for an autoimmune deficiency syndrome (eg, AIDS)
Data from references 1-9, 42, 51, 65-71.

dation of upper intake levels of vitamin D is 4000 IU/d for individuals 9 years and older,<sup>10</sup> reviews of reported cases of vitamin D toxicity and hypercalcemia have concluded that no observable adverse effects were noted even at doses of 10,000 IU/d.<sup>1-9,27,44,51,65,66</sup> However, the safety of long-term daily intakes of 10,000 IU of vitamin D is currently not known and therefore this intake level is inadvisable.

In the bloodstream, VBP transports vitamin D–related molecules. The serum concentration of VBP is 20 times higher than the amount of vitamin D metabolites. Approximately 99% of vitamin D metabolites are protein bound. As with many other hormones, the tissue availability of vitamin D is determined by the free fraction, and only the free fraction of vitamin D is metabolized. Decreased levels of VBP in states such as chronic liver diseases and nephrotic syndrome may therefore increase susceptibility to vitamin D toxicity.<sup>6</sup>

Management of vitamin D status in patients with sarcoidosis, many of whom have higher Fitzpatrick skin phototypes, represents a unique issue. A study of 59 patients with sarcoidosis showed that although many had inadequate 25(OH)D levels, determination of 1,25(OH)<sub>2</sub>D levels showed values at an adequate range.<sup>76</sup> Therefore, supplementation based on serum 25(OH)D values may inadvertently result in a hypervitaminosis D state.

An explanation for this observation is that interferon- $\gamma$  levels are elevated in sarcoidosis; interferon- $\gamma$  is known to mediate an increase in the activity of 1- $\alpha$  hydroxylase, the enzyme responsible for the conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D. Therefore, in patients with sarcoidosis, 1,25(OH)<sub>2</sub>D and PTH levels should be determined. Patients with low 1,25(OH)<sub>2</sub>D and normal PTH levels should receive supplementation with 400 to 800 IU/d of vitamin D<sub>3</sub>. For those with low 1,25(OH)<sub>2</sub>D and elevated PTH levels, consultation with an endocrinologist is recommended.<sup>76</sup>

#### HOW SHOULD WE ADVISE OUR PATIENTS ON VITAMIN D?

The IOM stated that a serum 25(OH)D level of 20 ng/mL is considered to cover the needs of 97.5% of the population.<sup>10</sup> However, many studies performed before November 2010 used a cutoff level of greater than 30 ng/mL. Therefore, the interpretation of data from these studies needs to be put in the context of the recent IOM recommendation. On the basis of the evidence discussed in this article, the following recommendations are appropriate for our patients:

1. Intake of vitamin D<sub>3</sub> supplements (600 IU/d for those 1-70 years old) is the most practical way of obtaining adequate vitamin D.<sup>10</sup>

2. For those who may be at risk for vitamin D deficiency (Table 3),<sup>1-9,42,51,65-69</sup> serum 25(OH)D determination is appropriate to assess the vitamin D status. We do not recommend testing vitamin D levels in individuals who are not at risk for deficiency.<sup>3,10,26</sup>
3. Adequate vitamin D supplementation theoretically could be achieved through dietary intake for healthy individuals. For example, an intake of 3.0 oz of salmon (450 IU of vitamin D) and 8 oz of vitamin D–fortified milk or orange juice (100 IU) will provide close to the recommended 600-IU/d dosage for a healthy adult.<sup>18</sup> Because of the scarcity of natural food sources rich in vitamin D, however, for most individuals, it is not practical to achieve adequate vitamin D intake from dietary sources alone.
4. It is inadvisable to use *intentional exposure* to UV radiation to improve vitamin D status because of the known photocarcinogenic adverse effects of natural and artificial UV radiation.<sup>52</sup>
5. Along with appropriate vitamin D supplementation, photoprotection (seeking shade, photoprotective clothing and hats, sunglasses, and sunscreens) should be practiced.<sup>44-46</sup>

#### CONCLUSION

Many aspects of vitamin D are relevant to dermatology and the broader field of medicine. Its potential benefits on skeletal health are well established; however, more research is needed to unravel its complicated ties to other human conditions. On the basis of currently available data, it is clear that dietary or supplemental vitamin D should be the preferred modern-day method of maintaining normal serum levels. Because of the known deleterious effects of solar and artificial UV radiation, UV exposure is not an appropriate way to achieve adequate vitamin D levels.

**Abbreviations and Acronyms:** 25(OH)D = 25-Hydroxyvitamin D; 1,25(OH)<sub>2</sub>D = 1,25-Dihydroxyvitamin D; AI = allowable intake; IOM = Institute of Medicine; IU = international units; MED = minimal erythema dose; ng/mL = nanograms/milliliter; nm = nanometer; nmol/L = nanomoles/Liter; SPF = sun protection factor; RDA = recommended dietary allowance; UV = ultraviolet; UV-A = ultraviolet A; UV-B = ultraviolet B; VBP = vitamin D binding protein

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