

# What You and Your Patients Need to Know About Vitamin D

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“Vitamin D” is the term commonly used to denote the lipid-soluble hormone critical for calcium homeostasis and skeletal maintenance. A precursor to the active compound is found in many plants and animal tissues and can be absorbed from the gut; it can also be derived from cell membranes in the epidermis during ultraviolet B irradiation. This compound is then hydroxylated sequentially in the liver and kidney to produce the active hormone 1,25(OH)<sub>2</sub>D that binds its nuclear receptor to modulate gene expression. Recently, vitamin D hydroxylases and the nuclear receptor have been identified in many tissues, suggesting previously unrecognized roles for vitamin D. Some epidemiologic studies have also correlated low levels of the inactive storage form 25(OH)D with an increased incidence or prevalence of a variety of diseases, suggesting that large oral supplements and/or increased ultraviolet (UV) exposure might therefore improve individual health. However, randomized, prospective controlled trials comparing vitamin D supplements with placebo have not supported this belief. Moreover, current evidence supports the conclusion that protection from UV radiation does not compromise vitamin D status or lead to iatrogenic disease. In contrast, high vitamin D levels appear to incur a risk of kidney stones and other adverse effects. In the case of true vitamin D deficiency, supplements are a more reliable and quantifiable source of the vitamin than UV exposure.  
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## Why We Care: The Vitamin D Controversy

In recent years, there has been a surge of interest in vitamin D, a lipid-soluble vitamin found in foods such as oily fish and milk and generated from epidermal cell membrane lipids during ultraviolet (UV) exposure (Fig. 1). Articles in seemingly every research journal have linked low levels of this vitamin to health concerns. Concomitantly, physician orders for vitamin D levels increased by more than 50% in the fourth quarter of 2009.<sup>1</sup> Moreover, vitamin D supplement sales increased from \$40 million in 2001 to \$550 million in 2010; in fact, vitamin D had the greatest increase in sales of any supplement in 2009.<sup>1-3</sup>

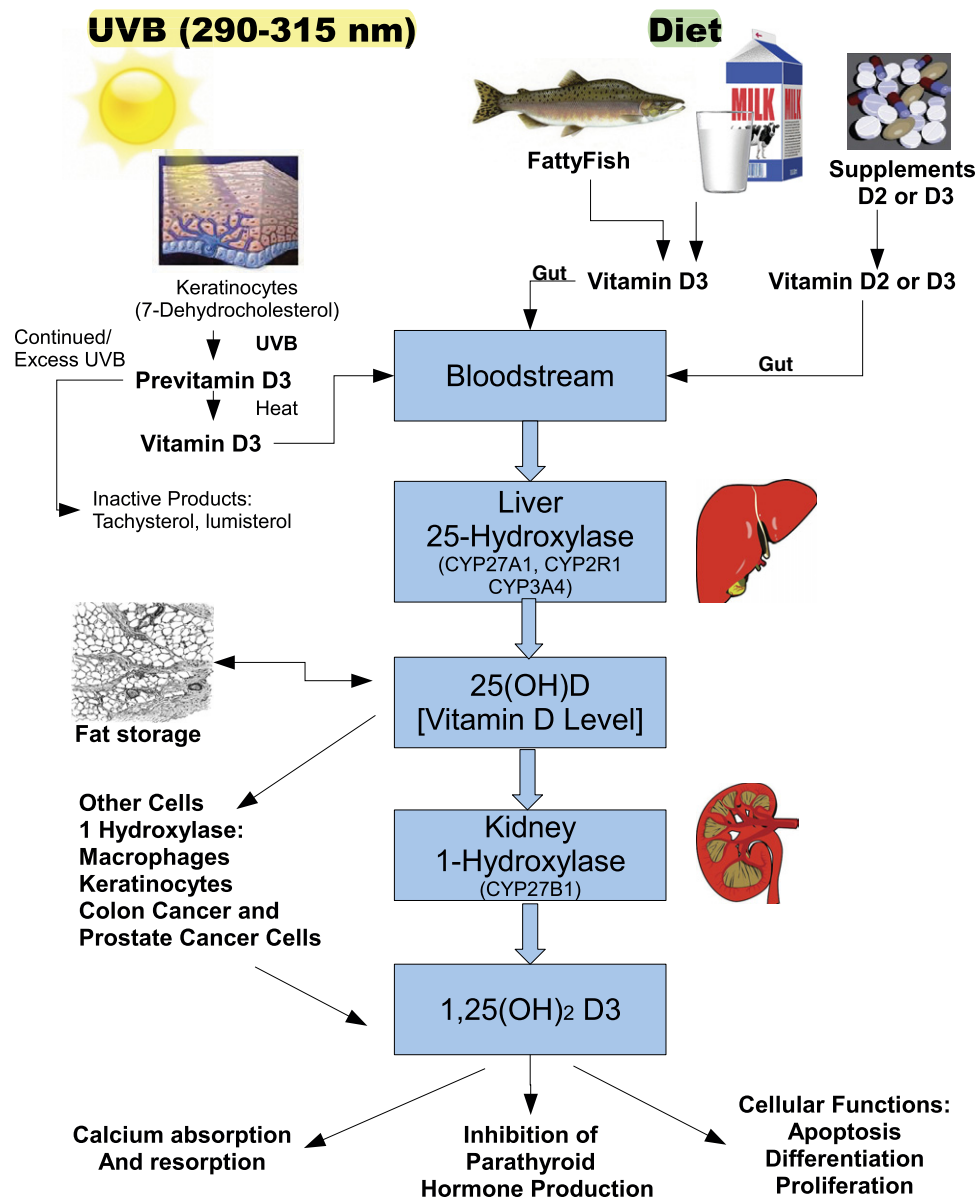
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Dermatologists and their patients have a particular interest in this issue because seeking vitamin D through UV exposure is perceived as incompatible with photoprotection, the major means of preventing skin carcinogenesis and photoaging. The public has associated sun exposure with health since the early 20th century when vitamin D synthesis through sun exposure was recognized to prevent and cure rickets.<sup>4</sup> At that time, patients with tuberculosis (TB) were treated with sunbathing, and home-based UV lamps were popularized.<sup>5</sup> More than 100 years later, sun exposure retains a reputation for health promotion among the lay public, greatly augmented by their desire to obtain a “healthy” attractive tan, as popularized by Coco Chanel in the 1920s. Consequently, the tanning industry has promulgated evidence of vitamin D health benefits as it seeks to profit from selling more UV exposure,<sup>5-7</sup> despite overwhelming evidence linking UV exposure to the development of cutaneous neoplasms and photoaging.

Clinicians and scientists have long hypothesized a link between UV radiation and skin cancer, and a causal relationship was documented in mouse models beginning in the 1930s. During the 1960s, UV radiation-induced DNA mutations were characterized, and recently, numerous target



**Figure 1** Sources and metabolism of vitamin D. (Modified from Reddy and Gilchrist. Iatrogenic effects of photoprotection recommendations on skin cancer development, vitamin levels and general health. *Exp Opin Dermatol*, in press.)

genes and signaling pathways have been identified.<sup>8</sup> The International Agency for Research on Cancer of the World Health Organization declared UV radiation, including that from artificial tanning devices, a class I carcinogen.<sup>9</sup> The American Academy of Dermatology and many international dermatologic organizations advocate against tanning bed use and excessive sun exposure to prevent or reduce skin cancers, including melanoma, and photodamage.<sup>10</sup> Each year, there are more than 3.5 million skin cancers diagnosed in the United States,<sup>11</sup> and in 2010, an estimated 114,900 new cases of melanoma.<sup>12</sup>

The purpose of this review is an attempt to provide dermatologists and their patients with information that separates the medical facts from poorly supported posturing about the “sunshine vitamin.” Specifically, we examine critical background concepts, including vitamin D terminology, how

photoprotection affects vitamin D synthesis, and the relationship between vitamin D and health metrics.

### What Is Vitamin D?

The term vitamin D is somewhat a misnomer because, unlike other essential vitamins and minerals, vitamin D can be made by the human body in addition to being taken in via diet and supplements. Two major forms include vitamin D<sub>2</sub> (ergocalciferol), derived from plants and often added to foods, and vitamin D<sub>3</sub> (cholecalciferol), the form synthesized from 7-dehydrocholesterol in the skin.<sup>13</sup> (The recent Institute of Medicine report on vitamin D requirements is summarized elsewhere.<sup>14</sup>) Studies suggest that D<sub>2</sub> and D<sub>3</sub> are functionally equivalent, but that vitamin D<sub>2</sub> is less stable than D<sub>3</sub>, at least in animal studies.<sup>13,15-17</sup> Once in the circulation, either form

of vitamin D is hydroxylated to 25(OH)D in the liver and then by 1-alpha-hydroxylase in the kidney, which results in 1,25(OH)<sub>2</sub>D, known as calcitriol (Fig. 1). Unlike 25(OH)D levels that vary markedly depending on dietary intake and sun exposure, 1,25(OH)<sub>2</sub>D levels are tightly regulated.<sup>13</sup> Renal synthesis is increased by parathyroid hormone (PTH), which is itself regulated by 1,25(OH)<sub>2</sub>D. PTH synthesis is decreased by fibroblast-like growth factor 23, which is known to increase during chronic kidney disease.<sup>13,18,19</sup> In a negative feedback loop, calcitriol inhibits the activity of 1-alpha-hydroxylase and increases the activity of 24-hydroxylase, which produces an inactive form of vitamin D, 24,25(OH)<sub>2</sub>D<sub>3</sub>,<sup>20</sup> further stabilizing the level of active hormone.

Vitamin D, or more correctly calcitriol, regulates serum calcium and phosphate in bone<sup>16,21,22</sup> by increasing intestinal calcium absorption, decreasing release of calcium from bone (via PTH), and stimulating reabsorption of calcium in the renal distal tubule (also via PTH).<sup>13</sup> However, the presence of vitamin D receptors in many tissues not involved in skeletal health suggests that vitamin D may have immunomodulatory, antiproliferative, or other effects.<sup>23,24</sup> At least 60 human cell types are known to express the vitamin D receptor, and more than 200 genes appear to be modulated by vitamin D.<sup>25</sup> Increasing calcitriol production in monocytes or macrophages increases production of cathelicidin, reducing susceptibility to *Mycobacterium tuberculosis*<sup>26</sup> and potentially other infections. Antiproliferative effects have been demonstrated that are mediated by changes in cyclin-dependent kinases, retinoblastoma protein phosphorylation, and repression of *myc*.<sup>27-33</sup>

Vitamin D<sub>3</sub> is synthesized in the skin after exposure to ultraviolet B (UVB) radiation at 290-315 nm, the same wavelengths most responsible for DNA damage and carcinogenesis.<sup>5</sup> Thus, sunscreen or dark skin pigmentation that absorbs these wavelengths would be expected to reduce such production. In addition, cutaneous vitamin D synthesis decreases with age, presumptively because of decreased 7-dehydrocholesterol release from cell membranes in an atrophic epidermis.<sup>34</sup> Cutaneous synthesis of vitamin D is self-limiting because during prolonged intense UV exposure, the newly generated previtamin D is converted to the inactive photo-products, eliminating the risk of vitamin D toxicity. The condition arises rarely from excess ingestion of the vitamin,<sup>35</sup> in part, because orally administered vitamin D is partially excreted via the feces.<sup>36,37</sup>

## What Is Enough: To Supplement or Not

Serum levels of 25(OH)D reflect the intake of vitamin D through food and supplements as well as cutaneous photosynthesis. Well-known sources of vitamin D include fatty fish, fish (cod) liver oil, and egg yolk; in the United States, some foods are also fortified (Table 1).<sup>13,38</sup> Absorption of dietary vitamin D requires intact systems for emulsification and hydrolyzing fat in the intestine. Patients with impaired bile acid release or pancreatic insufficiency therefore have

**Table 1 Dietary Sources of Vitamin D**

<b>Natural Sources*</b>	<b>Fortified Products†</b>	<b>Vitamin D (IU)</b>
Fresh wild salmon		600-1000
Fresh farmed salmon		100-250
Canned salmon		300-600
Sardines, canned		300
Mackerel, canned		250
Tuna, canned		224
Cod liver oil (1 tsp)		400-1600
Fresh shiitake mushrooms		100
Sun-dried shiitake mushrooms		1600
	Fortified milk	100
	Fortified orange juice	100
	Infant formulas	100
	Fortified yogurts	100
	Fortified butter (1 tbsp)	7
	Fortified margarine (1 tbsp)	61
	Fortified cheese (3.5 oz)	16
	Fortified breakfast cereal (1 cup)	100

Adapted from Holick.<sup>13,25</sup>

\*Per a 3.5-oz serving unless otherwise specified.

†Per an 8-oz serving unless otherwise specified.

decreased absorption of vitamin D.<sup>39-41</sup> In addition, weight-loss agents that impair fat absorption negatively affect vitamin D absorption.<sup>42,43</sup>

Measurements of serum 25(OH)D levels were found to assist in the evaluation of patients with clinical signs of rickets<sup>20</sup> and remain an important measure of vitamin D in certain other disease states. "Adequate" 25(OH)D levels are also a function of calcium availability and PTH function. Recently, however, much concern has arisen from medical and lay public reports of widespread vitamin D deficiency or insufficiency.<sup>13</sup>

By definition, vitamin D deficiency is a level that causes bone disease (rickets in children or osteomalacia in adults), usually equated with a 25(OH)D level of <10-20 ng/mL or 25-50 nmol/L.<sup>25,44</sup> (1 ng/mL = 2.5 nmol/L). The Institute of Medicine classifies vitamin D deficiency as a level below 12 ng/mL or 30 nmol/L. In vitamin D deficiency, associated clinical symptoms disappear rapidly after supplementation. On the other end of the spectrum, very high 25(OH)D levels are associated with hypercalcemia, vascular and soft-tissue calcification, nephrolithiasis, interference with iron and zinc ions in metabolic pathways, and constipation.<sup>13</sup> Vitamin D toxicity is rare and usually only occurs after supplementation with >10,000 IU daily, resulting in 25(OH)D levels above 150 ng/mL (375 nmol/L).<sup>20,37</sup> Any level between deficient and toxic is normal.

More recently, the concepts of vitamin D sufficiency and insufficiency have been put forward. Many authorities define

the range for insufficiency to be a 25(OH)D level of 10-30 ng/mL (25-75 nmol/L),<sup>20,45</sup> but some publications and Internet blogs recommend far higher levels<sup>46,47</sup> and even state that PTH must be maximally suppressed to attain vitamin D sufficiency.

Accordingly, some endocrinologists and nutritionists recommend daily vitamin D supplements of 1000-2000 IU daily.<sup>45</sup> However, based on a comprehensive and critical review of the literature, the Institute of Medicine report determined that adults have an estimated requirement of 400 IU daily and therefore a recommended daily allowance of 600 IU daily, increasing to 800 IU daily at >70 years of age. The recommended maximum intake for any adult is 4000 IU daily (Table 2),<sup>13</sup> in recognition of the health risks associated with very high levels. The report also concludes that for most people, the recommended daily allowance is easily achieved through diet alone without supplements or UV exposure.<sup>13</sup>

For those at risk of vitamin D deficiency, there are data that establish the efficacy of supplements at raising 25(OH)D levels. The Agency for Healthcare Research and Quality determined that for each additional 100 IU of vitamin D3 that is ingested, serum 25(OH)D concentrations increase by 1-2 nmol/L.<sup>48</sup> A study of veterans in the United States showed that oral cholecalciferol supplementation of 2000 IU daily for 6 months increased 25(OH)D levels from  $28.4 \pm 7.9$  to  $42.7 \pm 8.3$  ng/mL, a slightly smaller increase than predicted by that metric.<sup>49</sup>

The question arises whether vitamin D levels should be monitored at all in routine clinical practice. Many physicians have recently begun to do so, and testing for 25(OH)D has skyrocketed. However, the recommended treatment for vitamin D "insufficiency" is 800-1000 IU/d, which costs less than \$20/year, as compared with \$45-\$100 for the laboratory test.<sup>25,45,50</sup> It could therefore be argued that vitamin D testing is indicated only in cases when there are clinical signs and symptoms of vitamin D deficiency or toxicity, when there is a risk of fetal overexposure, or when there is a known risk factor, such as fat malabsorption, but that basically healthy adults, including those practicing safe sun, should simply use a daily supplement if there is any concern for vitamin D status.<sup>51</sup>

## How Does Photoprotection Affect Vitamin D Levels?

Factors that determine incident UVB dose and UVB absorption, scattering, or reflection affect cutaneous production of vitamin D. These include season, latitude, time of day, cloud cover, altitude, and use of sunscreen and other sun-protective measures. A study of women aged 65-77 in Omaha, Nebraska, demonstrated an average vitamin D level of 68 nmol/L (27.2 ng/mL) in February and 86 nmol/L (34.4 ng/nL) in August<sup>52</sup>; other studies have shown similar seasonal variations across the world. Individual levels are influenced by the level of skin pigmentation, as melanin absorbs UVB and results in smaller increases in 25(OH)D for a given UVB exposure; 25(OH)D levels in Canadians of European, East Asian, and South Asian ancestry were 71.7, 44.6, and 33.9 nmol/L at the end of the summer and 51.6, 28.1, and 26.5 nmol/L in late winter, respectively.<sup>53</sup> However, neither complexion nor latitude accurately predicts the average serum 25(OH)D level in a population,<sup>54</sup> as diet and lifestyle also play a major role.

Although sunscreens block UVB and therefore always decrease the rate of vitamin D production, they also always transmit a fraction of incident photons, as by definition sun protection factor (SPF) = 1/UVB transmission. That is, properly applied, an SPF 30 product transmits 1/30th or 3.3% of the energy responsible for sunburn and vitamin D photosynthesis. Furthermore, many studies have documented that sunscreen users customarily apply only 25%-50% of the recommended amount (0.5-1.0 vs 2 g/cm<sup>2</sup>).<sup>51</sup> The consequence is that regardless of intended SPF, most sunscreen users are actually exposed continuously to approximately 20% of the ambient UVB irradiation and hence produce vitamin D at approximately 20% of the rate in unprotected skin.<sup>51</sup> In practice, substantial vitamin D production occurs.<sup>55-57</sup> Mathematical models suggest that very modest sun exposure will result in adequate vitamin D production without specific efforts to seek out the sun.<sup>58</sup> Because net vitamin D photosynthesis is maximal after approximately one-third of a minimal erythema dose,<sup>25</sup> when the UV index is high, many individuals maximally produce vitamin D even while wearing a high SPF

**Table 2** Vitamin D Dietary Reference Intakes by Age

Age	Adequate Intake	Estimated Average Requirement	Recommended Daily Allowance	Upper Intake Level
0-6 months	400 IU	—	—	1000 IU
6-12 months	400 IU	—	—	1500 IU
1-3 years	—	400 IU	600 IU	2500 IU
4-8 years	—	400 IU	600 IU	3000 IU
9-70*	—	400 IU	600 IU	4000 IU
>70	—	400 IU	800 IU	4000 IU
Pregnancy	—	400 IU	600 IU	4000 IU
Lactation	—	400 IU	600 IU	4000 IU

\*Includes pregnant and lactating women.

Adapted from Institute of Medicine Report.<sup>13</sup>

sunscreen.<sup>51</sup> Of course, the body surface area that is irradiated also affects total production.<sup>59</sup>

Although photoprotection may somewhat reduce 25(OH)D levels, no data suggest that photoprotection leads to adverse health outcomes. In contrast, photoprotection is a proven method of reducing skin carcinogenesis. The United States Preventive Services Task Force review of the literature asserts that physician recommendations for sun protection do not place patients at significant risk for vitamin D deficiency.<sup>60</sup> For specific populations at risk, such as the elderly and those with darkly pigmented skin living in temperate climates, for whom cutaneous vitamin D production is inefficient in any case, oral supplementation is appropriate.<sup>51</sup>

## What Do Vitamin D Levels Mean for General Health?

There are many caveats relevant to the extensive vitamin D literature. First, articles with positive findings are more likely to get published and cited by those convinced that vitamin D insufficiency is a public health problem. Second, the housebound status of many individuals with serious illnesses may in part explain why their vitamin D levels are often lower than those of the general population and does not necessarily imply causation. A similar confounding factor is obesity, a state that is causally associated with many health problems, as well as with low serum levels of this fat-soluble vitamin.<sup>13</sup> There are also many poorly controlled studies that tie vitamin D to a number of diseases, presumably highlighted by the lay media because the subject is polarizing and catches readers' attention.

## Cancer

Studies related to cancer and vitamin D have been some of the most controversial and the most publicized. However, prospective randomized controlled trials (RCTs) and observational studies conducted during many years fail to support vitamin D supplementation as a means to reduce cancer incidence or mortality overall or by cancer subtype.<sup>13</sup> In addition, the national health and nutritional examination survey III study (1988-2006) showed that there was no overall reduction of cancer mortality associated with elevated 25(OH)D levels >100 nmol/L compared with <37.5 nmol/L. Although a subgroup analysis showed lower mortality rates from cancer in females in the summer/high latitude group, cancer mortality was increased among men with higher 25(OH)D levels, arguing against a physiological explanation for the statistical relationship in women.<sup>61</sup>

Cancer subtype-specific evidence also fails to support claims that vitamin D "sufficiency" is a risk reduction strategy for cancer. An 8-year follow-up study showed no effect of supplemental calcium and vitamin D on reducing risk for proliferative breast disease, a precursor of breast cancer.<sup>62</sup> Although *in vitro* studies document an antiproliferative response of prostatic carcinoma cells to vitamin D,<sup>63</sup> clinical studies have been inconclusive and contradictory with regard

to disease risk and 25(OH)D levels.<sup>64</sup> 25(OH)D levels were also not correlated with 3 head-and-neck cancer outcomes (recurrence, second primary cancer, and overall mortality).<sup>65</sup>

Of all the cancer subtypes, colorectal cancer has had the strongest statistical association with low 25(OH)D levels. Several epidemiologic studies report that higher levels are associated with lower incidence of colorectal cancer, as recently supported by a meta-analysis,<sup>66</sup> although the dose-response curve has not been established.<sup>13</sup> One observational study showed that a 25(OH)D level >75 nmol/mL was associated with a decreased risk of colorectal cancer.<sup>67</sup> However, in a prospective cohort study of stage IV colorectal cancer patients, although vitamin D deficiency or insufficiency was highly prevalent, there was no association between 25(OH)D status and disease outcome.<sup>68</sup> In addition, an RCT involving 36,282 postmenopausal women demonstrated no protective effect of daily vitamin D (400 IU) and calcium supplementation against colorectal cancer over at least 7 years.<sup>69</sup>

Although the data do not support causation, if vitamin D status is correlated with malignancy risk, it may be a proxy for another effect of UV exposure that is independent of vitamin D. A prospective cohort study looked at the risk for non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma in 121,216 persons in a California Teachers Study cohort.<sup>70</sup> Higher UV exposure, estimated based on the subjects' addresses and a National Solar Radiation database, was associated with a reduced risk for overall non-Hodgkin lymphoma (0.58), especially diffuse large B-cell lymphoma (0.36), as well as for chronic lymphocytic leukemia (0.46) and multiple myeloma (0.57). Dietary vitamin D was not associated with decreased risk, and 25(OH)D levels were not measured. The authors acknowledge that UV exposure raises risks for skin cancer and maintain that these data should be used to encourage research on the effect of UV on the immune system in lymphoid malignancies, not as a treatment recommendation.

The relationship between vitamin D and skin cancer is even more complex, and the implications for patients can be misleading. A recent post hoc analysis of data asserts that in women with a history of nonmelanoma skin cancer, calcium and vitamin D supplementation reduced melanoma risk, but these findings did not apply to the general population.<sup>71</sup> Moreover, a recent cohort study of 3223 white patients showed that a 25(OH)D level >15 ng/mL was positively correlated with nonmelanoma skin cancer with a 1.7 odds ratio.<sup>72</sup> These findings suggest that although vitamin D may have antiproliferative effects, the well-established causal effects of UV on skin cancer are more biologically significant.

## Cardiovascular Disease

A role for vitamin D in cardiovascular disease was suggested by the fact that there are more fatal cardiovascular events during the winter than the summer and in regions with less UVB.<sup>73</sup> However, the 1 RCT that looked at cardiovascular events and deaths for subjects given 100,000 IU of vitamin D every 4 months during a 5-year period showed no statistically significant change in adverse cardiovascular events and

deaths.<sup>74</sup> Although some observational studies have suggested a possible relationship, a critical review of the entire relevant literature does not support a beneficial effect of high 25(OH)D levels.<sup>13</sup> In addition, a recent meta-analysis of trials involving 29,000 persons showed that calcium supplements used with or without vitamin D modestly increase cardiovascular risk, although no studies examined data looking at vitamin D alone.<sup>75</sup> Moreover, an RCT in patients with heart failure did not show any improvement in quality of life or exercise capacity with vitamin D supplementation.<sup>76</sup>

Vitamin D is stored in adipose tissue, and overweight or obese patients, many with diabetes mellitus type II and metabolic syndrome, at known high risk of cardiovascular disease, tend to have lower levels of 25(OH)D.<sup>20</sup> Although observational studies of both retrospective and prospective nature support a link between low 25(OH)D and diabetes risk, the RCT data do not. For example, there was no change in blood glucose levels, blood pressure, or serum lipids in overweight or obese subjects who were supplemented with vitamin D over 1 year compared with unsupplemented control subjects, despite an increase in 25(OH)D level from 58 to 140 nmol/L.<sup>77</sup>

## Immune Function and Autoimmunity

Higher 25(OH)D levels are linked in some observational studies to a lower risk of type 1 diabetes, multiple sclerosis, and inflammatory bowel disease, as well as infectious diseases such as TB. However, the few RCTs are small studies with variable outcome measurements and do not demonstrate a dose-response relationship.<sup>13</sup> An RCT comparing conventional TB treatment supplemented with 2.5 mg (100,000 IU) of vitamin D3 given once daily vs placebo demonstrated that patients with the tt genotype of the *TaqI* vitamin D receptor polymorphism required significantly fewer days to achieve a negative sputum culture when receiving vitamin D, but no effect was seen in the whole study population.<sup>78</sup>

A recent observational study assessing prevalence of vitamin D deficiency in the elderly rheumatoid arthritis population showed that insufficiency defined as <30 ng/mL 25(OH)D was associated with higher tender joint counts and higher C-reactive protein levels,<sup>79</sup> but again RCTs are lacking.

Many studies have looked for relationships between vitamin D and autism, dementia, or mood disorders. Some observational studies support associations between low levels of 25(OH)D and calcium and poor cognitive function, but they are poorly controlled with small subject numbers.<sup>80</sup> A recent study also reported a high prevalence of hypovitaminosis D (<30 ng/mL 25(OH)D) in a Parkinson disease cohort, but 25(OH)D levels did not decline with disease severity, and there were no age-matched control subjects.<sup>81</sup> Given strong evidence that UV exposure upregulates beta-endorphins and that tanning has been demonstrated to be an addictive practice,<sup>82,83</sup> it is possible that higher 25(OH)D levels are associ-

ated with a lower risk of mood disorders. However, existing low-quality observational studies have variable results,<sup>84</sup> and higher quality studies do not exist.

Given that medications are best avoided if possible during pregnancy, efforts have been made to investigate vitamin D as a possible means for avoiding reproductive health problems. A few observational studies show an association between vitamin D supplements and reduced risk of preeclampsia, but RCTs have not.<sup>85,86</sup> RCTs looking at other reproductive outcomes, such as birth weight, have also not shown any benefit of vitamin D supplementation.<sup>87,88</sup>

## Musculoskeletal Health

Excellent data support a relationship of vitamin D status to skeletal health. In adults, optimal 25(OH)D status has been linked to positive changes in bone mineral density at the femoral neck.<sup>13</sup> Chung et al demonstrated via systematic review that supplementation with vitamin D3 (>800 IU/d) plus calcium (500 mg/d) increases the bone mineral density in the spine, total body, femoral neck, and total hip in menopausal women,<sup>89</sup> and such results have been corroborated by RCTs.<sup>90</sup> Although some RCTs have demonstrated that vitamin D plus calcium reduces the risk for fracture,<sup>74,91-96</sup> others have been unable to demonstrate benefit,<sup>97-108</sup> and 1 double-blind placebo-controlled trial looking at annual high-dose vitamin D supplementation (500,000 IU without calcium) in elderly women actually showed an increased risk of falls and fractures in the experimental group.<sup>109</sup> Ultimately, a 2009 Cochrane meta-analysis of 10 trials showed that vitamin D plus calcium supplementation in older persons reduces the risks of fracture (odds ratio, 0.89; 95% confidence interval, 0.80-0.99), although vitamin D alone did not.<sup>20,110</sup> With regard to falls, vitamin D doses of 800 IU/d are reported to improve physical performances measures,<sup>111</sup> but as with many of the health measures and vitamin D, RCTs are lacking.<sup>112</sup>

The Institute of Medicine report concludes that vitamin D plays a clear role in maintaining skeletal health but that no health benefits have been documented for maintaining 25(OH)D levels above the deficiency cutoff.<sup>13</sup> The report further concludes that apparently healthy people do not require supplementation or intentional sun exposure to maintain such levels. A recent Cochrane meta-analysis of 50 trials involving vitamin D supplementation demonstrated a mortality reduction of 6%, although supplementation also increased the risk of side effects, including nephrolithiasis and elevated blood calcium.<sup>113</sup> The authors advised supplementing only elderly women in institutionalized or dependent living with vitamin D3.<sup>113</sup> An ongoing 5-year, randomized, placebo-controlled trial involving 20,000 US men and women to determine the health effects of daily supplementation with 2000 IU of vitamin D and with and without n-3 fatty acids (Vitamin D and Omega-3 Trial; <http://ClinicalTrials.gov> number, NCT01169259)<sup>20</sup> should provide additional information and further refine recommendations in the future.

## Concluding Remarks

Despite the extensive recent media coverage, the established role of vitamin D in public health remains much the same as 100 years ago—a requirement for skeletal health, particularly relevant to debilitated elderly populations. Most adults with lighter skin easily maintain desirable 25(OH)D levels year-round by incidental protected sun exposure and a varied diet. Seeking vitamin D through sun exposure is an imprecise endeavor with well-documented risks of photocarcinogenesis and photoaging. Thus, persons at high or intermediate risk for skin cancer should practice “safe sun,” including wearing sun-protective clothing, use of SPF sunscreen, avoiding midday sun, and seeking shade. All persons should avoid recreational sun beds. Routine monitoring of 25(OH)D levels seems unwarranted; individuals concerned about possible deficiency or “insufficiency” should be encouraged to take a daily supplement of 400-1000 IU of vitamin D.

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